WEST Search History

DATE: Friday, May 16, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L8	L7 and l6 and l5	1	L8
L7	vasoconstrict$3	6064	L7
L6	anesthetic	17459	L6
L5	l3 and l4	65	L5
L4	botulinum toxin	387	L4
L3	L2 or l1	316	L3
L2	424/239.1	136	L2
L1	((424/236.1)!.CCLS.)	233	L1

END OF SEARCH HISTORY

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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Apr 08   "Ask CAS" for self-help around the clock
 NEWS  3  Apr 09   BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09   ZDB will be removed from STN
 NEWS  5  Apr 19   US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22   Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22   BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22   Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03   New e-mail delivery for search results now available
 NEWS 10  Jun 10   MEDLINE Reload
 NEWS 11  Jun 10   PCTFULL has been reloaded
 NEWS 12  Jul 02   FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22   USAN to be reloaded July 28, 2002;
                   saved answer sets no longer valid
 NEWS 14  Jul 29   Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30   NETFIRST to be removed from STN
 NEWS 16  Aug 08   CANCERLIT reload
 NEWS 17  Aug 08   PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08   NTIS has been reloaded and enhanced
 NEWS 19  Aug 19   Aquatic Toxicity Information Retrieval (AQUIRE)
                   now available on STN
 NEWS 20  Aug 19   IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 21  Aug 19   The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 22  Aug 26   Sequence searching in REGISTRY enhanced
 NEWS 23  Sep 03   JAPIO has been reloaded and enhanced
 NEWS 24  Sep 16   Experimental properties added to the REGISTRY file
 NEWS 25  Sep 16   Indexing added to some pre-1967 records in CA/CAPLUS
 NEWS 26  Sep 16   CA Section Thesaurus available in CAPLUS and CA
 NEWS 27  Oct 01   CASREACT Enriched with Reactions from 1907 to 1985
 NEWS 28  Oct 21   EVENTLINE has been reloaded
 NEWS 29  Oct 24   BEILSTEIN adds new search fields
 NEWS 30  Oct 24   Nutraceuticals International (NUTRACEUT) now available on STN
 NEWS 31  Oct 25   MEDLINE SDI run of October 8, 2002
 NEWS 32  Nov 18   DKILIT has been renamed APOLLIT
 NEWS 33  Nov 25   More calculated properties added to REGISTRY

 NEWS EXPRESS  October 14 CURRENT WINDOWS VERSION IS V6.01,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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STRUCTURE FILE UPDATES: 26 NOV 2002 HIGHEST RN 474607-46-0
DICTIONARY FILE UPDATES: 26 NOV 2002 HIGHEST RN 474607-46-0

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s botulinum toxin
516 BOTULINUM
12102 TOXIN
L1 9 BOTULINUM TOXIN
(BOTULINUM(W)TOXIN)

=> d l1

L1 ANSWER 1 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN 256438-74-1 REGISTRY
CN G protein (guanine nucleotide-binding protein) (human fetal skin gene rac1 isoform Rac1b) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN G protein (guanine nucleotide-binding protein) (human gene Rac1 isoform Rac1b)
CN Phosphatase, guanosine tri- (human gene RAC1 isoenzyme Rac1b)
CN **Ras-related C3 botulinum toxin substrate (human gene Rac1 isoform Rac1b)**
CN Small GTPase rac1b (human fetal skin gene rac1 isoform Rac1b)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> d l1 2-9

L1 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN 225458-22-0 REGISTRY
CN DNA (human fetal skin gene rac1 G protein (guanine nucleotide-binding protein) isoform Rac1b cDNA) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5043: PN: WO0153836 TABLE: 6 claimed DNA
CN 505: PN: WO0146697 TABLE: 21 claimed DNA
CN 7782: PN: WO0142792 TABLE: 8A-1 claimed DNA
CN DNA (human clone WO0118542_SEQID_1158 ovary tumor-associated protein cDNA)
CN DNA (human fetal skin gene rac1 small GTPase rac1b isoform Rac1b cDNA)
CN DNA (human gene Rac1 G protein (guanine nucleotide-binding protein) isoform Rac1b cDNA)
CN **DNA (human gene Rac1 ras-related C3 botulinum toxin substrate isoform Rac1b cDNA)**
CN PN: WO0118542 SEQID: 1158 claimed DNA
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
6 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 3 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN 127315-80-4 REGISTRY
CN Protein (human clone 5 gene rac2 reduced) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 13: PN: WO9958669 SEQID: 13 unclaimed protein
CN 44: PN: WO9958670 SEQID: 52 unclaimed protein
CN **Protein DJ151B14.2 (ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)) (human clone RP1-151B14 gene dJ151B14.1)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
5 REFERENCES IN FILE CA (1962 TO DATE)
5 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 4 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN 107231-16-3 REGISTRY
CN Botulin G (9CI) (CA INDEX NAME)

OTHER NAMES:
CN Botulin toxin G
CN **Botulinum toxin G**
CN Toxin, botulin, G
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
              54 REFERENCES IN FILE CA (1962 TO DATE)
               3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
              54 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 5 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN 107231-13-0 REGISTRY
CN Botulin C1 (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Botulinum toxin C1**
CN C1 botulin toxin
CN Toxin, botulin, C1
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
              57 REFERENCES IN FILE CA (1962 TO DATE)
               3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
              57 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 6 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN 93384-47-5 REGISTRY
CN Botulin E (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Botulinum toxin E**
CN Toxin, botulin, E
MF Unspecified
CI MAN
SR Commission of European Communities
LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, CHEMCATS, CHEMLIST, CSCHEM,
      TOXCENTER, USPAT2, USPATFULL
    Other Sources: EINECS**
        (**Enter CHEMLIST File for up-to-date regulatory information)

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             178 REFERENCES IN FILE CA (1962 TO DATE)
               5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             178 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 7 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN 93384-46-4 REGISTRY
CN Botulin D (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Botulin toxin D
CN **Botulinum toxin D**
CN Toxin, botulin, D
MF Unspecified
CI MAN
SR Commission of European Communities
LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, CHEMLIST, CSCHEM, RTECS*,
      TOXCENTER, USPAT2, USPATFULL
        (*File contains numerically searchable property data)
    Other Sources: EINECS**

(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
95 REFERENCES IN FILE CA (1962 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
95 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 8 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN 93384-44-2 REGISTRY
CN Botulin B (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Botulin toxin B
CN **Botulinum toxin B**
CN Myobloc
CN NeuroBloc
MF Unspecified
CI MAN
SR Commission of European Communities
LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, CHEMCATS, CHEMLIST, CIN, CSCHEM, IPA, MRCK*, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
235 REFERENCES IN FILE CA (1962 TO DATE)
7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
235 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN 93384-43-1 REGISTRY
CN Botulin A (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Botox
CN Botulin neurotoxin A
CN Botulin toxin A
CN **Botulinum toxin A**
CN **Botulinum toxin type A**
CN Dysport
CN Oculinum
MF Unspecified
CI MAN
SR Commission of European Communities
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, DRUGNL, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
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Other Sources: EINECS**
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601 REFERENCES IN FILE CA (1962 TO DATE)
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601 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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=> s l1
  25 FILES SEARCHED...
L2   12186 L1

=> s botulinum
L3   54772 BOTULINUM

=> s l2 or l3
L4   54912 L2 OR L3

=> s local anesthetic
L5   93949 LOCAL ANESTHETIC

=> s l4 and l5
L6   173 L4 AND L5

=> s vasoconstrictor
L7   84946 VASOCONSTRICTOR

=> s l6 and l7
L8 2 L6 AND L7

=> d l8 1-2 ibib, kwic

L8 ANSWER 1 OF 2 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002057500 EMBASE
TITLE: **Botulinum** toxin to minimize facial scarring.
AUTHOR: Sherris D.A.; Gassner H.G.
CORPORATE SOURCE: Dr. D.A. Sherris, Division of Facial Plastic Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States
SOURCE: Facial Plastic Surgery, (2002) 18/1 (35-39).
Refs: 17
ISSN: 0736-6825 CODEN: FPSUEA
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 009 Surgery
013 Dermatology and Venereology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
TI **Botulinum** toxin to minimize facial scarring.
AB **Botulinum** toxin injection has been used for a variety of indications in humans, including blepharospasm and hyperfunctional facial lines. This article describes a novel formulation of **botulinum** toxin, which supplies immediate feedback to the injecting physician. Additionally, recent findings are described that indicate the immediate injection of **botulinum** toxin into the muscles underlying a wound can improve the cosmetic outcome of the facial cutaneous scar. Future applications of. . .
CT Medical Descriptors:
*scar . . . therapy
*scar formation: PC, prevention
*skin scar: CO, complication
*skin scar: DT, drug therapy
*skin scar: PC, prevention
face surgery
plastic surgery
wound healing
esthetics
tension
drug effect
drug efficacy
human
nonhuman
male
clinical trial
adult
review
***botulinum toxin A: CT, clinical trial**
***botulinum toxin A: AD, drug administration**
***botulinum toxin A: CB, drug combination**
***botulinum toxin A: DO, drug dose**
***botulinum toxin A: DT, drug therapy**
***botulinum toxin A: IM, intramuscular drug administration**
***local anesthetic agent: CT, clinical trial**
***local anesthetic agent: AD, drug administration**
***local anesthetic agent: CB, drug combination**
***local anesthetic agent: DO, drug dose**
***local anesthetic agent: IM, intramuscular drug administration**
***vasoconstrictor agent: CT, clinical trial**
***vasoconstrictor agent: AD, drug administration**

***vasoconstrictor agent: CB, drug combination**
***vasoconstrictor agent: DO, drug dose**
***vasoconstrictor agent: IM, intramuscular drug administration**
*lidocaine: CT, clinical trial
*lidocaine: AD, drug administration
*lidocaine: CB, drug combination
*lidocaine: DO, drug dose
*lidocaine: IM, intramuscular drug. . .
RN (**botulinum** toxin A) **93384-43-1**; (lidocaine) 137-58-6, 24847-67-4, 56934-02-2, 73-78-9; (adrenalin) 51-43-4, 55-31-2, 6912-68-1

L8 ANSWER 2 OF 2 USPATFULL

ACCESSION NUMBER:	2000:121520 USPATFULL		
TITLE:	Method for treating painful conditions of the anal region and compositions therefor		
INVENTOR(S):	Fogel, Barry S., Waban, MA, United States		
PATENT ASSIGNEE(S):	Synchroneuron, LLC, Waban, MA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6117877		20000912
APPLICATION INFO.:	US 1999-258828		19990225 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-31858, filed on 27 Feb 1998		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Cook, Rebecca		
LEGAL REPRESENTATIVE:	Choate, Hall & Stewart		
NUMBER OF CLAIMS:	22		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1104		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . determined by the intensity of the contraction of the IAS. These treatments include lateral sphincterotomy, injection of the sphincter with **botulinum** toxin (Maria et al., Ann Surg, 1998 November, 228(5):664-9), and application of nitroglycerin ointment (Manookian et al.; Ann Surg 1998. . . . of treatment for chronic anal fissures recommends beginning with nitroglycerin ointment. If the fissure has not healed in six weeks, **botulinum** toxin injections are given. That review notes that "considerable educational effort is required to successfully adjust the dose" of nitroglycerin. . .

SUMM . . . minutes. A separate approach, described by Parischa and Kallo in U.S. Pat. No. 5,437,291, makes use of direct injections of **botulinum** toxin into the affected area for treatment of gastrointestinal muscle disorders and other smooth muscle dysfunction. They report that the benefits of **botulinum** toxin injection appear to be sustained for several months.

SUMM . . . blocker together with sucralfate. Yet another aspect is a composition comprising a combination of an .alpha.-adrenergic blocker together with a **local anesthetic** (preferably lidocaine). In addition, the inventive composition may combine .alpha.-adrenergic blocker, together with sucralfate and a **local anesthetic** to achieve a synergistic effect. These compositions have analgesic properties and are useful for treatment of anal fissures and other. . .

SUMM . . . an uncomfortable sense of fecal urgency in an individual with a painful anal condition. Capsaicin can be co-administered with a **local anesthetic** agent to diminish the burning sensation that accompanies its initial application to skin or mucosa. In other preferred embodiments, any. . .

DETD Three factors contribute to the synergistic efficacy of the combination: 1) the **local anesthetic** effect of lidocaine is based

on a different mechanism of action than the analgesic effect of nitroglycerin; 2) sucralfate serves. . .

DETD In one preferred embodiment, the .alpha.1-adrenergic blocker is used alone. Alternatively the .alpha.1-adrenergic blocker is combined with a **local anesthetic** for treatment of painful anal conditions. One skilled in the art will recognize any **local anesthetic**, such as, without limitation, lidocaine, benzocaine, dibucaine bupivacaine, tetracaine etc., is acceptable for use in the present invention. Preferred local anesthetics include lidocaine, benzocaine, dibucaine, and bupivacaine. A most preferred **local anesthetic** is lidocaine.

DETD . . . and pharmacodynamic properties. In yet another preferred embodiment of the present invention, the .alpha.-adrenergic blocker is combined with both a **local anesthetic** and sucralfate or similar anti-inflammatory, as mentioned above, for application to the anal region.

DETD . . . of terazosin or doxazosin would be administered in the dose range of 0.1-1.0 mg per 5 ml of formula. A **local anesthetic** of the same potency as lidocaine would be administered at a concentration in the dose range of 20-200 mg per. .

DETD . . . mucous membranes (see Case Report 6), especially mucous membranes of the anal region. More preferably, capsaicin is combined with a **local anesthetic** at such dose that the capsaicin is effective at reducing pain in the anal region, yet is tolerable upon application.. . . depletion of Substance P from the local. In a particularly preferred embodiment, capsaicin (at a tolerable dose or with a **local anesthetic**) is combined with an .alpha.1-adrenergic antagonist for treatment of anal pain.

DETD . . . the combination of .alpha.-adrenergic blocker with an additional active ingredient can be enhanced further by the addition of either a **local anesthetic**, sucralfate or both. Such compositions may be applied to the anal region at effective and non-toxic dosages for treatment of. . .

DETD . . . one, preferably any two of a steroidal antiinflammatory (e.g., a corticosteroid), a non-steroidal antiinflammatory drug (including specifically diclofenac opiates), a **local anesthetic** , sucralfate or a similar disaccharide, capsaicin (with a **local anesthetic**, i.e., lidocaine) or capsaicin (in a tolerable dosage or preparation). Such combinations would provide improved relief over treatment with the. . .

DETD . . . (i.e., an .alpha.1-adrenergic antagonist or a non-specific .alpha.-adrenergic antagonists with sufficient .alpha.1-adrenergic antagonist effects.). Alternatively, capsaicin, with or without a **local anesthetic** such as lidocaine, can be used to replace the active agents or ingredients in the above-mentioned marketed over-the-counter compositions.

DETD . . . symptoms of anorectal disease are formulated in the same composition, for example with a wound healing compound, a protectant, a **vasoconstrictor**, or a **local anesthetic** or with more than one of these compounds.

DETD Tolerability of Capsaicin in a Formula Containing a **Local Anesthetic**

DETD Conclusion: Administration of 0.075% capsaicin cream alone to the anal region is intolerable, but if it is combined with a **local anesthetic** ingredient that reduces the initial burning sensation, it becomes tolerable. Once it is made tolerable by the concurrent presence of a **local anesthetic**, capsaicin, with its known local analgesic properties, becomes a safe and effective active ingredient in a composition for the relief. . .

DETD . . . and lidocaine is particularly effective. Preparations of superior effectiveness combine an agent that relieves spasm of the IAS with a **local anesthetic** and with an agent with antiinflammatory and/or protective properties. 2) Nontoxic doses of

alpha 1-adrenergic blockers, such as doxazosin, can. . . . Capsaicin, which by itself is intolerable by the rectal route of administration, becomes tolerable when given in combination with a **local anesthetic**. It thus can be a useful addition to a composition for the treatment of anorectal pain, as long as that composition contains a **local anesthetic** ingredient.

DETD A triple combination of nitroglycerin, sucralfate, and lidocaine (or more generally a nitrate, sucralfate, and a **local anesthetic**) will produce more rapid, complete, and long-lasting relief than a composition with only one or two of the three ingredients. A triple combination of an alpha 1-adrenergic blocker, sucralfate, and a **local anesthetic** will produce more rapid, complete and long-lasting relief than a composition with only one or two of the three ingredients.. . .

CLM What is claimed is:

. . . anal region associated with muscle spasm, the method comprising steps of: providing a composition comprising an .alpha.-adrenergic blocker and a **local anesthetic**; and applying an effective dose of the composition to the anal region.

. . . the anal region associated with muscle spasm, the method comprising steps of: providing a composition comprising an .alpha.-adrenergic blocker, a **local anesthetic** and sucralfate; and applying an effective dose of the composition to the anal region.

. . . the anal region associated with muscle spasm, the method comprising steps of: providing a composition comprising an .alpha.-adrenergic blocker, a **local anesthetic** and capsaicin; and applying an effective dose of the composition to the anal region.

10. The method of claim 3, 4 or 5, wherein the **local anesthetic** is selected from the group consisting of: lidocaine, benzocaine, bupivacaine, and tetracaine.

. . . the anal region associated with muscle spasm, the method comprising steps of: providing a composition comprising an .alpha.-adrenergic blocker, a **local anesthetic** and sucralfate in a base of petrolatum, and further comprising a water soluble lubricant; and applying an effective dose of. . .

18. The method of claim 16 wherein the **local anesthetic** is lidocaine.

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=> file home
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               51.31      75.64

FILE 'HOME' ENTERED AT 11:31:29 ON 27 NOV 2002

=> d his

     (FILE 'HOME' ENTERED AT 11:13:14 ON 27 NOV 2002)

     FILE 'REGISTRY' ENTERED AT 11:13:29 ON 27 NOV 2002
L1            9 S BOTULINUM TOXIN

     FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT,
     CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL,
     EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF,
     MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 11:16:15 ON 27 NOV 2002
L2        12186 S L1
L3        54772 S BOTULINUM
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L4         54912 S L2 OR L3
L5         93949 S LOCAL ANESTHETIC
L6           173 S L4 AND L5
L7         84946 S VASOCONSTRICTOR
L8             2 S L6 AND L7

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=> FIL MEDICINE
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                               ENTRY    SESSION
FULL ESTIMATED COST                             0.84      76.48

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FILE 'USPAT2' ENTERED AT 11:34:03 ON 27 NOV 2002
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L1            9 S BOTULINUM TOXIN

     FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT,
     CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL,
     EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF,
     MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 11:16:15 ON 27 NOV 2002
L2        12186 S L1
L3        54772 S BOTULINUM
L4        54912 S L2 OR L3
L5        93949 S LOCAL ANESTHETIC
L6          173 S L4 AND L5
L7        84946 S VASOCONSTRICTOR
L8            2 S L6 AND L7

     FILE 'HOME' ENTERED AT 11:31:29 ON 27 NOV 2002

     FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT,
     CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL,
     EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF,
     MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 11:34:03 ON 27 NOV 2002

=> s l4 and l7
L9           27 L4 AND L7

=> dup rem
ENTER L# LIST OR (END):l9
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGLAUNCH,
DRUGMONOG2, KOSMET, MEDICONF, PHARMAML'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L9
L10           20 DUP REM L9 (7 DUPLICATES REMOVED)

=> d l10 1-20 ti

L10  ANSWER 1 OF 20  USPATFULL                              DUPLICATE 1
TI     UPREGULATION OF TYPE III ENDOTHELIAL CELL NITRIC OXIDE SYNTHASE BY
       AGENTS THAT DISRUPT ACTIN CYTOSKELETAL ORGANIZATION

L10  ANSWER 2 OF 20     MEDLINE
TI   Botulinum neurotoxin A attenuates release of norepinephrine but
     not NPY from vasoconstrictor neurons.

L10  ANSWER 3 OF 20  JICST-EPlus COPYRIGHT 2002 JST
TI   Augmenting Mechanism of Slowly Developing Contractile Response to the
     Stimulation of Thromboxane A2-Receptor in the Middle Cerebral Artery of
     Bovine.

L10  ANSWER 4 OF 20  EMBASE  COPYRIGHT 2002 ELSEVIER SCI. B.V.
TI   Botulinum toxin to minimize facial scarring.

L10  ANSWER 5 OF 20  USPATFULL
TI     Methods and compositions for the regulation of vasoconstriction

L10  ANSWER 6 OF 20  USPATFULL
TI     Upregulation of Type III endothelial cell nitric oxide synthase by rho
       GTPase function inhibitors

L10  ANSWER 7 OF 20     MEDLINE
TI   Human urotensin II-induced contraction and arterial smooth muscle cell
     proliferation are mediated by RhoA and Rho-kinase.

L10  ANSWER 8 OF 20  JICST-EPlus COPYRIGHT 2002 JST
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TI Role of Rho-kinase in the Serotonin-Induced Contraction of the Middle Cerebral Artery of Bovine.

L10 ANSWER 9 OF 20 USPATFULL
TI Preparation for the application of agents in mini-droplets

L10 ANSWER 10 OF 20 USPATFULL
TI Method for treating painful conditions of the anal region and compositions therefor

L10 ANSWER 11 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
TI Addditon of an anesthetic agent to enhance the predictability of the effects of **botulinum** toxin type A injections: A randomized controlled study.

L10 ANSWER 12 OF 20 SCISEARCH COPYRIGHT 2002 ISI (R)
TI Different levels of immunoreactivity for synaptosomal-associated protein of 25 kDa in **vasoconstrictor** and vasodilator axons of guinea-pigs

L10 ANSWER 13 OF 20 MEDLINE
TI Cholinergic modulation of non-adrenergic, non-cholinergic relaxation in isolated, small coronary arteries from lambs.

L10 ANSWER 14 OF 20 USPATFULL
TI Aptamers specific for biomolecules and methods of making

L10 ANSWER 15 OF 20 CANCERLIT DUPLICATE 3
TI Tyrosine phosphorylation as a convergent pathway of heterotrimeric G protein- and rho protein-mediated Ca2+ sensitization of smooth muscle of rabbit mesenteric artery.

L10 ANSWER 16 OF 20 MEDLINE
TI Botulinolysin, a thiol-activated hemolysin produced by Clostridium **botulinum**, inhibits endothelium-dependent relaxation of rat aortic ring.

L10 ANSWER 17 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
TI Mechanism of alpha-2-adrenergic receptor coupling to phospholipase D in PC 12 cells.

L10 ANSWER 18 OF 20 DRUGU COPYRIGHT 2002 THOMSON DERWENT
TI Pharmaceutical market 1993. (Question.). What was really new. Part I.

L10 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5
TI Mechanism of the local vascular actions of 1,1-dimethyl-4-phenylpiperanium (DMPP), a potent ganglionic stimulant

L10 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
TI Effects of nicotine on the blood vessels of skeletal muscle in the cat. An investigation of vasomotor axon reflexes

=> d l10 11-11 ibib, kwic

L10 ANSWER 11 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2000:382652 BIOSIS
DOCUMENT NUMBER: PREV200000382652
TITLE: Addditon of an anesthetic agent to enhance the predictability of the effects of **botulinum** toxin type A injections: A randomized controlled study.

AUTHOR(S): Gassner, Holger G.; Sherris, David A. (1)
CORPORATE SOURCE: (1) Department of Otorhinolaryngology, Mayo Clinic, 200 First St SW, Rochester, MN, 55905 USA
SOURCE: Mayo Clinic Proceedings, (July, 2000) Vol. 75, No. 7, pp. 701-704. print.
ISSN: 0025-6196.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Addditon of an anesthetic agent to enhance the predictability of the effects of **botulinum** toxin type A injections: A randomized controlled study.
AB Objectives: To determine whether the paralyzing effect of **botulinum** toxin type A reconstituted in a solution of lidocaine with epinephrine is as effective as that of the same toxin reconstituted in saline and to determine whether the addition of lidocaine with epinephrine enhances the predictability of outcomes of **botulinum** toxin injections. Subjects and Methods: This double-blind, within-subject, randomized controlled study was conducted in 10 volunteer subjects. Lidocaine was added to **botulinum** toxin type A to achieve an immediate paralyzing effect on the injected muscle, and epinephrine was added to minimize diffusion. . . 5 to 10 minutes, 1 week, and 3 months after the injections. Results: Immediate paralysis ensued on the experimental side (**botulinum** toxin type A + lidocaine + epinephrine) in all 10 volunteers. As assessed by 3 blinded evaluators, the extent of immediate paralysis resulting from the anesthetic agent was predictive of the extent of delayed paralysis resulting from the **botulinum** toxin. The **botulinum** toxin-induced paralysis wore off symmetrically in all subjects. Conclusion: The injection of **botulinum** toxin reconstituted in lidocaine with epinephrine provided the physician immediate feedback on the extent of paralysis to be expected from the chemodenervating action of the **botulinum** toxin. This may enhance the safety and predictability of **botulinum** toxin injections in many applications.
IT . . .
Systems of Organisms
corrugator supercilii muscle: muscular system; frontalis muscle: muscular system; procerus muscle: muscular system
IT Chemicals & Biochemicals
botulinum toxin type A: chemodenervating effects, injection, outcome predictions, paralytic, predictability, reconstitution solution, safety; epinephrine: **vasoconstrictor**; lidocaine: general anesthetic - drug

=> d l10 4-4 ibib, kwic

L10 ANSWER 4 OF 20 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002057500 EMBASE
TITLE: **Botulinum** toxin to minimize facial scarring.
AUTHOR: Sherris D.A.; Gassner H.G.
CORPORATE SOURCE: Dr. D.A. Sherris, Division of Facial Plastic Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States
SOURCE: Facial Plastic Surgery, (2002) 18/1 (35-39).
Refs: 17
ISSN: 0736-6825 CODEN: FPSUEA
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 009 Surgery
013 Dermatology and Venereology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

TI **Botulinum** toxin to minimize facial scarring.
AB **Botulinum** toxin injection has been used for a variety of indications in humans, including blepharospasm and hyperfunctional facial lines. This article describes a novel formulation of **botulinum** toxin, which supplies immediate feedback to the injecting physician. Additionally, recent findings are described that indicate the immediate injection of **botulinum** toxin into the muscles underlying a wound can improve the cosmetic outcome of the facial cutaneous scar. Future applications of. . .
CT Medical Descriptors:
*scar . . . therapy
*scar formation: PC, prevention
*skin scar: CO, complication
*skin scar: DT, drug therapy
*skin scar: PC, prevention
face surgery
plastic surgery
wound healing
esthetics
tension
drug effect
drug efficacy
human
nonhuman
male
clinical trial
adult
review
***botulinum toxin A: CT, clinical trial**
***botulinum toxin A: AD, drug administration**
***botulinum toxin A: CB, drug combination**
***botulinum toxin A: DO, drug dose**
***botulinum toxin A: DT, drug therapy**
***botulinum toxin A: IM, intramuscular drug administration**
*local anesthetic agent: CT, clinical trial
*local anesthetic agent: AD, drug administration
*local anesthetic agent: CB, drug combination
*local anesthetic agent: DO, drug dose
*local anesthetic agent: IM, intramuscular drug administration
***vasoconstrictor agent: CT, clinical trial**
***vasoconstrictor agent: AD, drug administration**
***vasoconstrictor agent: CB, drug combination**
***vasoconstrictor agent: DO, drug dose**
***vasoconstrictor agent: IM, intramuscular drug administration**
*lidocaine: CT, clinical trial
*lidocaine: AD, drug administration
*lidocaine: CB, drug combination
*lidocaine: DO, drug dose
*lidocaine: IM, intramuscular drug. . .
RN (**botulinum** toxin A) **93384-43-1**; (lidocaine) 137-58-6, 24847-67-4, 56934-02-2, 73-78-9; (adrenalin) 51-43-4, 55-31-2, 6912-68-1

=> d l1- 5-5 ibib, kwic
'L1-' IS NOT A VALID FORMAT
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REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):end

=> d l10 5-5 ibib, kwic

L10 ANSWER 5 OF 20 USPATFULL

ACCESSION NUMBER: 2001:205895 USPATFULL
TITLE: Methods and compositions for the regulation of vasoconstriction
INVENTOR(S): Waeber, Christian, Boston, MA, United States
Moskowitz, Michael A., Belmont, MA, United States
Yoshimura, Shin-Ichi, Zurich, Switzerland
Salomone, Salvatore, Somerville, MA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001041688	A1	20011115
APPLICATION INFO.:	US 2001-804987	A1	20010313 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-188859P	20000313 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, c/o Wolf, Greenfield & Sacks, P.C., Federal Reserve Plaza, 600 Atlantic Avenue, Boston, MA, 02210-2211
NUMBER OF CLAIMS: 85
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 2803
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . synergist; thyroid hormone; thyroid inhibitor; thyromimetic; treatment of amyotrophic lateral sclerosis; treatment of Paget's disease; treatment of unstable angina; uricosuric; **vasoconstrictor**; vasodilator; vulnerary; wound healing agent; xanthine oxidase inhibitor. In an important embodiment, the second therapeutic agent is TPA.
DETD . . . was from Sigma, C. difficile toxin B was from List Biological Laboratories. 7.5 .mu.g (in 66 .mu.l water) of C. **botulinum** C.sub.3 exoenzyme (Biomol) were mixed with 25 .mu.g liposome (Transfectam, Promega), resuspended in 0.5 ml physiological solution and applied directly. . .
DETD . . . treated, in vitro, with bacterial toxins specifically affecting G.sub.i/o (B. Pertussis toxin) or Rho (C. Difficile toxin B or C. **Botulinum** C.sub.3 exoenzyme). Incubation with Pertussis toxin did not modify the S1P-induced vasoconstriction, but (as expected) decreased the response to the. . .
DETD . . . did not modify the contractile response to 5-HT (not shown). These results indicate that at least EDG-3 receptor mediates the **vasoconstrictor** response to S1P in cerebral blood vessels.
DETD . . . J. R., et al., J. Biol. Chem. 274: 4626-4632 (1999)) The present study provides evidence that S1P is a preferential **vasoconstrictor** in cerebral arteries. The **vasoconstrictor** effect in cerebral arteries occurs, in vitro, in the submicromolar range (S1P's EC.sub.50 for rat basilar artery: 280 nM, Table. . .

=> d l10 9-9 ibib, kwic

L10 ANSWER 9 OF 20 USPATFULL
ACCESSION NUMBER: 2000:174129 USPATFULL
TITLE: Preparation for the application of agents in mini-droplets
INVENTOR(S): Cevc, Gregor, Heimstetten, Germany, Federal Republic of
PATENT ASSIGNEE(S): Idea AG, Munich, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 6165500	20001226
APPLICATION INFO.:	US 1992-844664	19920408 (7)

PRIORITY INFORMATION:	NUMBER	DATE
	DE 1990-4026834	19900824
	DE 1990-4026833	19900824
	DE 1991-4107153	19910306
	WO 1991-EP1596	19910822

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Kishore, Gollamudi S.
LEGAL REPRESENTATIVE:	Davidson, Davidson & Kappel, LLC
NUMBER OF CLAIMS:	35
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	31 Drawing Figure(s); 21 Drawing Page(s)
LINE COUNT:	4336

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . aflatoxin B2-alpha, aflatoxin G1, aflatoxin G2, aflatoxin G2-alpha, aflatoxin M1, aflatoxin M2, aflatoxin P1, aflatoxin Q1, alternariol-monomethyl ether, aurovertin B, **botulinum** toxin D, cholera toxin, citreoviridin, citrinin, cyclopiazonic acid, cytochalasin A, cytochalasin B, cytochalasin C, cyrochalasin D, cytochalasin, cytochalasin H, cytochalasin. . .

CLM What is claimed is:

. . . a protein, a protein derivative, an anti-psoriatic, a psychostimulant, a sleep-inducing agent, a sedating agent, a spasmolytic, atuberculosis preparation, a **vasoconstrictor**, a vasodilator, a wound-healing substance and a combination thereof.

=> d his

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L1 9 S BOTULINUM TOXIN

FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 11:16:15 ON 27 NOV 2002

L2 12186 S L1
L3 54772 S BOTULINUM
L4 54912 S L2 OR L3
L5 93949 S LOCAL ANESTHETIC
L6 173 S L4 AND L5
L7 84946 S VASOCONSTRICTOR
L8 2 S L6 AND L7

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FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 11:34:03 ON 27 NOV 2002

L9 27 S L4 AND L7
L10 20 DUP REM L9 (7 DUPLICATES REMOVED)

=> s epinephrine or adrenalin or phenylephrine
L11 339813 EPINEPHRINE OR ADRENALIN OR PHENYLEPHRINE

```
=> s bupivicaine or lidocaine or mepivicaine or ?caine
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'ADISALERTS'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'ADISINSIGHT'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'ADISNEWS'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'CEN'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'DGENE'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'DRUGB'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'DRUGLAUNCH'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'DRUGMONOG2'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'DRUGNL'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'DRUGU'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'EMBAL'
  16 FILES SEARCHED...
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'ESBIOBASE'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'IFIPAT'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'IPA'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'JICST-EPLUS'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'KOSMET'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'LIFESCI'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'NLDB'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'PASCAL'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'PHARMAML'
  32 FILES SEARCHED...
L12     382445 BUPIVICAINE OR LIDOCAINE OR MEPIVICAINE OR ?CAINE
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> d his

     (FILE 'HOME' ENTERED AT 11:13:14 ON 27 NOV 2002)

     FILE 'REGISTRY' ENTERED AT 11:13:29 ON 27 NOV 2002
L1            9 S BOTULINUM TOXIN

     FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT,
     CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL,
     EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF,
     MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 11:16:15 ON 27 NOV 2002
L2        12186 S L1
L3        54772 S BOTULINUM
L4        54912 S L2 OR L3
L5        93949 S LOCAL ANESTHETIC
L6          173 S L4 AND L5
L7        84946 S VASOCONSTRICTOR
L8            2 S L6 AND L7

     FILE 'HOME' ENTERED AT 11:31:29 ON 27 NOV 2002

     FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT,
     CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL,
     EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF,
     MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 11:34:03 ON 27 NOV 2002
L9            27 S L4 AND L7
L10           20 DUP REM L9 (7 DUPLICATES REMOVED)
L11       339813 S EPINEPHRINE OR ADRENALIN OR PHENYLEPHRINE
L12       382445 S BUPIVICAINE OR LIDOCAINE OR MEPIVICAINE OR ?CAINE
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=> s l4 and l11 and l12
L13          76 L4 AND L11 AND L12

=> dup rem
ENTER L# LIST OR (END):l13
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGLAUNCH,
DRUGMONOG2, KOSMET, MEDICONF, PHARMAML'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L13
L14           67 DUP REM L13 (9 DUPLICATES REMOVED)

=> s composition
  33 FILES SEARCHED...
L15     3156465 COMPOSITION

=> s l14 and l15
  28 FILES SEARCHED...
L16          50 L14 AND L15

=> d l16 1-50 ibib, kwic

L16  ANSWER 1 OF 50  USPATFULL
ACCESSION NUMBER:        2002:291895  USPATFULL
TITLE:                   Electrokinetic delivery of medicaments
INVENTOR(S):             Henley, Julian L., New Haven, CT, United States
                         Chang, Kuo Wei, Waltham, MA, United States
                         Potter, Joseph, Oak Bluffs, MA, United States
                         Goldberg, Dennis I., Boston, MA, United States
                         Porter, Christopher H., Woodinville, WA, United States
                         Porcelli, V. Lorenzo, Ossining, NY, United States
PATENT ASSIGNEE(S):      BioPhoretic Therapeutic Systems, LLC, Framingham, MA,
                         United States (U.S. corporation)

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 6477410          B1   20021105
APPLICATION INFO.:       US 2000-584138           20000531  (9)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            GRANTED
PRIMARY EXAMINER:        Walberg, Teresa
ASSISTANT EXAMINER:      Dahbour, Fadi H.
LEGAL REPRESENTATIVE:    Nixon & Vanderhye
NUMBER OF CLAIMS:        47
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      35 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT:              2235
SUMM    . . . benzothiadiazides, beta blockers, antiarrythmics
        beta-adrenergic agonists, beta-adrenergic antagonists, selective
        beta-one-adrenergic antagonists, selective beta-two-adreneric
        antagonists, bile salts, medicaments affecting volume and
        composition of body fluids, butyrophenones, agents affecting
        calcification, catecholamines and sympathomimetics, cholergic agonists,
        cholinesterase reactivators, dermatological medicaments,
        diphenylbutylpiperines, diuretics, ergot alkaloids,. . .
SUMM    . . . leuprolide, octreotide, endorphin, TRH, NT-36(-[[(s)-4-oxo-2-
        azetidinyl]carbonyl]-L-histidyl-L-prolinamide), liprecin, LMW heparin,
        i.e., enoxaparin, melatonin, medrysone, 6.alpha.-methylprednisolone,
        mometasone, paramethasone, prednisolone, prednisone, tetrahydrocortisol,
        trimcinolone, benoxinate, benzocaine, bupivacaine,
        chloroprocaine, dibucaine, dyclonine,
        etidocaine, mepivacaine, pramoxine, procaine
        , proparacaine, tetracaine, chloroform, cloned,
        cycloproane, desflurane, diethyl ether, droperidol, enflurane,
```

etomidate, halothane, isoflurane, ketamine, hydrochloride, meperidine, methohexital, methoxylflurane, nitrogylcerine, propofol, scvoflurane, thiamyal,. . . sulindae, tometin, acetophenazine, chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, triflurperazine, trifluprornazine, disopyramide, encainide, flecinide, indecainide, mexiletine, moricizine, phenytoin, procainamide, propafenone, quinidine, **tocaine**, cisapride, domperdone, dronabinol, haloperidol, metoclopramide, nabilone, nicotine, prochlorperazine, promethazine, thiethylperazine, trimethobenzamide, buprenorphine, butorphanol, codeine, dezocine, diphenoxylate, drocode, doxazosin, hydrocodone, hydromorphone, levallorphan, levorphanol, lopermide, meptazinol, methadone, nalbuphine, nalmefene, naloxone, naltrexone, oxybutynin, oxycodone, oxymorphone, pentazocine, propoxyphene, isosobide, dinitrate, nitroglycerin, theophylline, **phenylephrine**, ephedrine, pilocarpine, furosemide, tetracycline, chlorpheniramine, ketorolac, bromocriptine, guanabenz, prazisin, doxazosin, and flufenamic acid.

SUMM . . . agents, e.g., collagen, reactive monomers which may polymerize under the skin in non aqueous carriers and be activated by water, **botulinum** toxins, e.g. botox, bleaching agents, e.g., Eldopaque 4% by ICN Pharmaceuticals, or a combination of Ketorolac, hydroquinone 4%, Glycolic Acid, lactic acid with suitable vehicle and anesthetics, such as **lidocaine**, **xylocaine**, **prontocaine**, **prilocaine**, fetanyl, remifentanil, sufentanil, alfentanil, **novocaine**, **procaine**, morphine HCL and EMLA either in stand alone fashion or with a vasodilator such as **epinephrine**. Also, medicaments which inhibit fusion between the plasma membrane and viruses and other adventitious agents to prevent entry by viruses. . . such as bactracin, Diprolene, topical steroids, and the like, aloe or aloe containing products or OTC products such as Ambesol, **Lanocaine** and the like, other wound healing agents, such as epidermoid derived growth factors as well as peptides that modulate the. . .

L16 ANSWER 2 OF 50 USPATFULL

ACCESSION NUMBER:	2002:272506 USPATFULL		
TITLE:	Lipid-protein-sugar particles for drug delivery		
INVENTOR(S):	Kohane, Daniel S., Newton, MA, UNITED STATES Lipp, Michael, Framingham, MA, UNITED STATES Langer, Robert S., Newton, MA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002150621	A1	20021017
APPLICATION INFO.:	US 2001-981020	A1	20011016 (9)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2000-240636P		20001016 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Choate, Hall & Stewart, Exchange Place, 53 State Street, Boston, MA, 02109		
NUMBER OF CLAIMS:	79		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	12 Drawing Page(s)		
LINE COUNT:	1953		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . are also provided. Methods of providing a nerve block are also provided by administering LPSPs with a local anesthetic (e.g., **bupivacaine**) within the vicinity of a nerve.

SUMM . . . particles have the additional advantage of protecting the drug from degradation by the body. These particles depending on their size, **composition**, and the drug being delivered can be administered to an individual using any route available.

SUMM . . . number of approaches have been tried (for example, see Boedecker et al. "Ultra-long-duration local anesthesia produced by injection of lecithin-coated **tetracaine** microcrystals" J. Clin. Pharmacol. 34:699-702, 1994; Curley et al. "Prolonged regional nerve blockade. Injectable biodegradable **bupivacaine**/polyester microspheres" Anesthesiology 84:1401-1410, 1996; Grant et al. "Prolonged analgesia with liposomal **bupivacaine** in a mouse model" Reg. Anesth. 19:264-269, 1994; Kirkpatrick et al. "Long duration local anesthesia with lecithin-coated microdroplets of methoxyflurane:. . .

SUMM . . . of administering a nerve block. The agent to be delivered may be an anesthetic such as an amine-amide-containing anesthetic (e.g., **bupivacaine**, **lidocaine**). LPSPs containing these agents may be delivered in the vicinity of a nerve to provide local anesthesia of a desired. . .

SUMM . . . amount of LPSPs may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the **composition** of the encapsulating matrix, the target tissue, etc. For example, the effective amount of LPSPs containing a local anesthetic to. . .

DRWD [0023] FIG. 2 shows the cumulative release from a dialysis tube of **bupivacaine** encapsulated in 10% (w/w) **bupivacaine** lipid-protein particles with 60% (.circle-solid.) or 99% (.box-solid.) of the excipients being dipalmitoylphosphatidylcholine, or an equivalent amount of 0.5% (w/v) **bupivacaine** in solution (.DELTA.). Also shown is release from 50% (w/w) **bupivacaine** PLGA microsphere (O). Data shown are means with standard deviations. n=4 for all points.

DRWD [0024] FIG. 3 shows the comparison of the durations of sensory and motor blockade for 10% (w/w) **bupivacaine** lipid-protein (.circle-solid.), 50% (w/w) **bupivacaine** PLGA microspheres (0), and 0.5% (w/v) **bupivacaine** in solution (.DELTA.). Points falling above the diagonal line bisecting the graph represent a relative sensory predominance in nerve blockade,. . .

DRWD . . . the time course of thermal latency in the uninjected leg following sciatic nerve block in animals injected with 10% (w/w) **bupivacaine** lipid-protein particles (.circle-solid.) and in animals injected with 50% (w/w) **bupivacaine** PLGA microspheres (O). Here thermal latency in the uninjected (contralateral) leg is used as a measure of systemic drug distribution.. . .

DETD [0034] The present invention provides a system including a pharmaceutical **composition** of lipid-protein-sugar particles (LPSP) containing an agent as well as methods of preparing and administering the LPSPs. Agents administered using. . .

DETD . . . the agent is a local anesthetic. Particularly preferred anesthetics are amine-amide containing anesthetics. Anesthetics include, but are not limited to, **lidocaine**, **procaine**, **dibucaine**, **tetracaine**, **bupivacaine**, **mepivacaine**, **benzocaine**, **etidocaine**, **prilocaine**, **ropivacaine**, **proparacaine**, pramoxine, **chloroprocaine**, **cocaine**, and **articaine**.

DETD . . . combination with a anti-inflammatory agent such as a steroid. Local anesthetics may also be administered with vasoactive agents such as **epinephrine**. To give but another example, an antibiotic may be combined with an inhibitor of the enzyme commonly produced by bacteria. . .

DETD . . . bacterial organisms as Streptococccus pnuemoniae, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pyrogenes, Corynebacterium diphtheriae, Listeria monocytogenes, Bacillus anthracis, Clostridium tetani, Clostridium **botulinum**, Clostridium perfringens, Neisseria meningitidis, Neisseria gonorrhoeae, Streptococcus mutans, Pseudomonas aeruginosa, Salmonella typhi, Haemophilus parainfluenzae, Bordetella pertussis, Francisella tularensis, Yersinia pestis,. . .

DETD . . . etc. One of ordinary skill in the art may test a variety of

ratios and specific components to determine the **composition** correct for the desired purpose. Any known lipid, protein, and sugar, natural or unnatural, may be used to prepare the. . .

DETD . . . etc.). The protein may be chosen based on known interactions between the protein and the agent being delivered. For example, **bupivacaine** is known to bind to albumin in the blood; therefore, albumin would be a logical choice in choosing a protein from which to prepare microparticles containing **bupivacaine**. The percentage of protein in the matrix (excluding the agent to be delivered) may range from 0% to 99%, more. . .

DETD [0058] Once the LPSPs have been prepared, they may be combined with other pharmaceutical excipients to form a pharmaceutical **composition**. As would be appreciated by one of skill in this art, the excipients may be chosen based on the route. . .

DETD . . . coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the **composition**, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and/or to. . .

DETD . . . coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a **composition** that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a. . .

DETD [0068] Dosage forms for topical or transdermal administration of an inventive pharmaceutical **composition** include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, or patches. The LPSPs are admixed under sterile conditions with. . .

DETD . . . conditions (e.g., solvent, temperature, concentration, air flow rate, etc.) used may also depend on the agent being encapsulated and/or the **composition** of the matrix.

DETD . . . Any of the methods described above may be used in preparing the inventive LPSPs. Specific methods of preparing LPSPs containing **bupivacaine** are described below in the Examples.

DETD [0079] In one particularly preferred embodiment, LPSPs containing a local anesthetic (e.g., **bupivacaine**, **lidocaine**, **mepivacaine**) are administered in the vicinity of a nerve to provide a nerve block. Nerve blocks provide a method of anesthetizing. . . intercostal nerves, nerves of the cervical plexus, median nerve, ulnar nerve, and sensory cranial nerves. In a particularly preferred embodiment, **epinephrine** or another vasoactive agent is administered along with the local anesthetic to prolong the block. The **epinephrine** or other agent (e.g., other vasoactive agents, steroidal compounds, non-steroidal anti-inflammatory compounds) may be encapsulated in the LPSPs containing the. . .

DETD Sciatic Nerve Blockade with Lipid-Protein-Sugar Particles Containing **Bupivacaine**

DETD . . . tetrodotoxin for prolonged anesthesia" Anesthesiology 89:119-131, 1998; Thalhammer et al. "Neurologic evaluation of the rat during sciatic nerve block with **lidocaine**" Anesthesiology 82:1013-1025, 1995; each of which is incorporated herein by reference) that examines sensory (thermal nociception) and motor (weight bearing). . . in the peripheral nervous system and spinal cord (Castillo et al. "Glucocorticoids prolong rat sciatic nerve blockade in vivo from **bupivacaine** microspheres" Anesthesiology 85:1157-1166, 1996; Curley et al. "Prolonged regional nerve blockade. Injectable biodegradable **bupivacaine**/polyester microspheres" Anesthesiology 84:1401-1410, 1996; Drager et al. "Prolonged intercostal nerve blockade in sheep using controlled release **bupivacaine** and dexamethasone from polyester microspheres" Anesthesiology 89:969-979, 1998; Estebe et al. "Prolongation of spinal anesthesia with **bupivacaine**-loaded (DL-lactide) microspheres" Anesth. Analg 81:99-103, 1995; Le Corre et al. "Preparation and characterization of **bupivacaine**-loaded polylactide and polylactide-coglycolide

microspheres" Int. J. Pharmaceut. 107:41-49, 1994; Le Corre et al. "In vitro controlled release kinetics of local. . . Pharm. Bull. 29:3363-3368, 1981; Wakiyama et al. "Preparation and evaluation in vitro and in vivo of polylactic acid microspheres containing **dibucaine** " Chem. Pharm. Bull. 30:3719-3727, 1982; each of which is incorporated herein by reference), and b) such microspheres have been described as producing very slow release of local anesthetics (Curley et al. "Prolonged regional nerve blockade. Injectable biodegradable **bupivacaine**/polyester microspheres" Anesthesiology 84:1401-1410, 1996; incorporated herein by reference).

DETD [0084] **Bupivacaine** hydrochloride, human serum albumin (Fraction V), and lactose .beta.-monohydrate were purchased from Sigma Chemical Co. (St. Louis, Mo.), L-.alpha.-dipalmitoylphosphatidylcholine (DPPC). . . and methylene chloride (both HPLC grade) from EM Sciences (Gibbstown, N.J.), and USP grade ethanol from Pharmco Products, Brookfield, Conn. **Bupivacaine** hydrochloride was made into the free base by alkaline precipitation and filtration. The ultraviolet absorbance spectrum from 200 nm to. . .

DETD [0086] A 70:30 (v/v) ethanol:water solvent system was employed for solubilization and spray drying of excipients and **bupivacaine**. The solutions were prepared in the following manner: (i) the DPPC and **bupivacaine** free base were dissolved in a given amount of ethanol, (ii) the lactose and albumin were dissolved in a given. . . .

DETD . . . drying airflow rate, and aspirator pressure) were optimized based on the yield and size characteristics of both the blank (no **bupivacaine**) and the **bupivacaine**-containing particles. The optimized conditions were: inlet temperature=115 to 120.degree. C., solution feed rate=12 to 14 ml/min, drying airflow rate=600 l/min,. . .

DETD [0092] **Bupivacaine** Content of LPSPs

DETD [0093] In order to determine the **bupivacaine** content of LPSPs, 10 mg of particles were agitated (Touch Mixer model 2332, Fisher Scientific, Pittsburgh, Pa.) for 20 seconds. . . at 272 nm was then measured (Cary 50 Bio UV-Visible Spectrophotometer, Varian, Australia) in a quartz cuvette (Hellma, Mullheim, Germany). **Bupivacaine** content was determined by comparison to a standard curve. Blank (no **bupivacaine**) LPSPs served as controls, and when processed in this manner had negligible absorbance at 272 nm. As an additional control we determined the amount of albumin that may have accompanied the **bupivacaine** in the ethyl acetate extraction (this was important because the two compounds have overlapping absorbance spectra), using a commercial kit. . .

DETD [0094] In vitro Release of **Bupivacaine** from Microparticles

DETD . . . (Ames Aliquot Mixer, Miles). At predetermined intervals, the dialysis bag was transferred to a test tube with fresh PBS. The **bupivacaine** concentration in the dialysate was quantitated by measuring absorbance at 272 nm and referring to a standard curve. Observation of. . .

DETD [0096] Preparation and Characterization of PLGA-**Bupivacaine** Microspheres

DETD [0097] Microspheres loaded with 10% (w/w) and 50% (w/w) **bupivacaine** were prepared using a single emulsion method (Curley et al "Prolonged regional nerve blockade. Injectable biodegradable **bupivacaine**/polyester microspheres" Anesthesiology 84:1401-1410, 1996; Watts et al. "Microencapsulation using emulsification/solvent evaporation: an overview of techniques and applications" Crit. Rev. Ther. Drug Carr. Sys. 7:235-259, 1990; each of which is incorporated herein by reference). **Bupivacaine** and PLGA were dissolved in methylene chloride, and the mixture was homogenized (Silverson L4R, Silverson Machines Ltd., Cheshire, England) in. . .

DETD [0098] **Bupivacaine** content was determined by dissolving 10 mg of microspheres in 1 ml methylene chloride, and comparing the resulting UV absorbance at 272 nm to a standard curve. Under similar conditions, PLGA microspheres containing no **bupivacaine** showed negligible

absorbance at 272 nm.

DETD . . . greater trochanter, pointing in an anteromedial direction (Thalhammer et al. "Neurologic evaluation of the rat during sciatic nerve block with **lidocaine**" Anesthesiology 82:1013-1025, 1995; incorporated herein by reference). Once bone was contacted, the needle was withdrawn 1 mm and the particle-containing. . .

DETD . . . applying the methods of Thalhammer et al. (Thalhammer et al. "Neurologic evaluation of the rat during sciatic nerve block with **lidocaine**" Anesthesiology 82:1013-1025, 1995; incorporated herein by reference), or modifications thereof (Kohane et al. "A re-examination of tetrodotoxin for prolonged anesthesia". . .

DETD . . . of blank excipient particles (60:20:20 DPPC:albumin:lactose), as discussed in the methods section. (The reported percentage of DPPC refers to the **composition** of the excipients, excluding the delivered drug.) These conditions also appeared to be satisfactory for the production of the 10% (w/w) **bupivacaine** particles with varying DPPC contents. The results obtained from typical runs are shown in Table 1.

TABLE 1

Characteristics of lipid-protein-sugar particles (LPSPs) and PLGA-based microspheres

Microparticle	DPPC (%.sup.a)	**Bupivacaine** loading (%)	n	Yield.sup.b, (%)	c Median diameter.sup.b, d (.mu.m)	**Bupivacaine**.sup.b, e (%)
LPSP	3	10	5	40 .+-. 6	2.58 .+-. 0.22	8 .+-. 0.4

. . .

DETD . . . over a period of 4 weeks storage in a dessicator, while those of 60% DPPC particles did not change. The **bupivacaine** content of the various LPSPs formulations was similar (p=n.s.).

DETD [0116] Production and Characterization of PLGA-**Bupivacaine** Microspheres

DETD . . . particle yield was comparable to that of the spray-dried particles. The data relevant to the production of the 10% (w/w) **bupivacaine** microspheres were similar to those for the 50% (w/w) microspheres, and their mean **bupivacaine** content (w/w) was 8% (n=2).

DETD [0118] **Bupivacaine** Release from LPSPs

DETD . . . suspension in phosphate buffered saline, while 60% and 99% particles lasted many days. Consequently, we focused on the latter preparations. **Bupivacaine** release from 50 mg samples of 10% loaded (w/w) **bupivacaine**-LPSPs (n=4 for each particle formulation) was measured. FIG. 2 shows the cumulative release of **bupivacaine** over time. Both particle types caused delayed release of **bupivacaine** into the dialysate compared to the unencapsulated drug (1 ml of 0.5% (w/v) **bupivacaine**, or 5 mg). Both 60% and 99% DPPC particles completely released their **bupivacaine** content within 24 hours. However, release from the 60% DPPC particles was more gradual: at 9 hours, the 60% DPPC particles had released 53.8.+-.1.5% of their **bupivacaine** content, whereas the 99% DPPC particles had released 80.6.+-.4.7% (p=0.0002). Consequently, the 60% DPPC formulation was selected for in vivo studies. FIG. 2 also shows the release of **bupivacaine** from 50% (w/w) PLGA particles (n=4). The release, on a percentage basis, was much slower than that from LPSPs: less. . . that released by PLGA microspheres at most early time points (by 3.5 hours, the LPSPs had released 1.65.+-.0.17 mg of **bupivacaine** vs. 1.26.+-.0.15 mg for PLGA microspheres, p=0.01). This relationship was reversed at longer durations (by 9 hours the LPSPs had released 2.6.+-.0.2 mg of **bupivacaine**, compared to 4.2.+-.0.7 mg for the PLGA microspheres (p=0.02)).

DETD [0122] Rats were injected at the sciatic nerve with 75 mg (.apprxeq.215 mg/kg) of spray-dried LPSPs containing 10% (w/w) **bupivacaine**, and the time course of nerve blockade was followed. All rats injected with 10% (w/w) **bupivacaine** LPSPs achieved maximal nerve block (thermal latency.apprxeq.12 seconds) by the time of the first testing (30 minutes). Four out of ten rats injected with 50% **bupivacaine** microspheres did not achieve maximal block by that time. Nine out of ten rats injected with 50% (w/w) **bupivacaine** microspheres had maximal block by one hour after injection. All achieved maximal block within 3 hours.

DETD [0123] The average duration of thermal nociceptive block from 10% (w/w) **bupivacaine** LPSPs was 468.+-.210 min (n=10). The duration of thermal nociceptive block obtained from injection with 75 mg of PLGA microspheres with 50% (w/w) loading of **bupivacaine** was 706 344 min (n=10). This was not statistically different from the duration obtained with the 10% (w/w) **bupivacaine** LPSPs (p=0.08).

DETD [0124] In order to compare the efficacy of equal loading with **bupivacaine**, rats were injected with 75 mg of 10% (w/w) **bupivacaine** PLGA microspheres (n=5), and 50% (w/w) **bupivacaine** LPSPs (n=2). The former did not result in nerve block as defined by our paradigm, while the latter caused rapid. . .

DETD . . . order to verify that the increased efficiency (comparable duration of block with much lower drug loading) of the LPSPs over **bupivacaine** microspheres was not due to an intrinsic nerve blocking-effect of the component excipients. Blank LPSPs did not produce any detectable. . .

DETD [0127] Blank LPSPs and 10% (w/w) **bupivacaine** microspheres did not cause any impairment in sensory or motor function. Motor blockade from 10% (w/w) **bupivacaine** LPSPs lasted 508.+-.258 min, while that from 50% (w/w) **bupivacaine** microspheres lasted 1062.+-.1456 min (p=0.005). FIG. 3 focuses on the clinically important comparison of the durations of motor block (x-axis). . .

DETD [0128] Systemic Distribution of **Bupivacaine**

DETD . . . leave his paw on the hotplate) was measured in the un-injected leg at predetermined intervals, in rats who received 10% **bupivacaine** LPSPs or 50% **bupivacaine** microspheres (FIG. 4). There was no statistically significant difference between the mean latencies in the two groups at any time. . .

DETD [0130] One rat (out of 11) injected with 50% **bupivacaine** microspheres died, approximately 2 hours after injection. Necropsy revealed congestion of the liver and kidneys, most consistent with heart failure. Both rats injected with 50% (w/w) **bupivacaine** LPSPs died. There were no deaths in the 10% (w/w) **bupivacaine** LPSP group (n=10), or 10% (w/w) PLGA microsphere group.

DETD [0131] Encapsulation improved the safety and efficacy of **bupivacaine**. None of the rats injected with 10% (w/w) **bupivacaine** LPSPs had marked increases in contralateral latency. In comparison, rats (n=6) injected with an equivalent amount of **bupivacaine** in solution (1.5 ml of 0.5% **bupivacaine**, i.e. 7.5 mg) had a duration of block of 166.+-.55 min. For this experiment larger rats (approx. 410 g) were. . . than those used in the remainder of the study, in order to avoid animal death (the median lethal dose of **bupivacaine** in adult rats is 30.+-.5 mg/kg (Kohane et al. "Sciatic nerve blockade in infant, adolescent, and adult rats: a comparison of **ropivacaine** and **bupivacaine**" Anesthesiology 89:1199-1208, 1998; incorporated herein by reference), or 10.5 mg in a 350 g rat). Even so, one of those. . . of systemic toxicity (thermal latency=12 seconds in the uninjected leg). It was not possible to directly compare the efficacy of **bupivacaine** solution and 50% **bupivacaine** microspheres, since the dose of **bupivacaine** contained in 75 mg of those microspheres (38.5 mg) is approximately three times the median lethal dose of the unencapsulated drug (Kohane et al. "Sciatic nerve blockade in infant, adolescent, and adult rats: a comparison of **ropivacaine** and

bupivacaine" Anesthesiology 89:1199-1208, 1998). Nevertheless, it is obvious that the microspheres increased the safety of **bupivacaine**.

DETD . . . Of the three LPSP formulations tested in vitro, the 60% DPPC particles appeared optimal in terms of drug release of **bupivacaine**. The slower release of **bupivacaine** from the 60% DPPC particles compared to the 99% DPPC particles was somewhat surprising; a priori one might have expected. . . may impede access of water to the encapsulated drug and of drug to the exterior, or to a degree of **bupivacaine** binding by albumin.

DETD . . . of local anesthesia, with one-fifth the initial loading of drug. (The duration of block that we obtained with the 50% **bupivacaine** microspheres is considerably longer than previously published values. Seventy-five percent loaded particles have been reported to last 6.0.+-.3.0 hours (Curley et al. "Prolonged regional nerve blockade. Injectable biodegradable **bupivacaine**/polyester microspheres" Anesthesiology 84:1401-1410, 1996; incorporated herein by reference), compared to 11.8.+-.5.7 hours for the 50% loaded particles in this study.). . . would be that the LPSPs themselves have an effect on nerve function. While this possibility cannot be excluded, LPSPs without **bupivacaine** did not cause any detectable deficits in nerve function.

DETD . . . of severe local anesthetic toxicity (Kohane et al. "Sciatic nerve blockade in infant, adolescent, and adult rats: a comparison of **ropivacaine** and **bupivacaine**" Anesthesiology 89:1199-1208, 1998; incorporated herein by reference).) The in vitro data suggest that this was because the discrepancy in total. . . as great as the fractional (percentage) difference. PLGA microspheres would appear to provide a better margin of safety at high **bupivacaine** loadings.

DETD . . . return before motor function. In the case of the PLGA microspheres, the rate of decline of the local concentration of **bupivacaine** is probably slower, so that the time interval between the termination of sensory blockade and motor blockade is longer. The. . . kinetic argument for the difference between the functional selectivities of LPSPs and PLGA microspheres is supported by the observation that **bupivacaine** solution (in the absence of any controlled release device) also shows approximately equal durations of sensory and motor block (FIG.. . . noted in this animal model (Kohane et al. "Sciatic nerve blockade in infant, adolescent, and adult rats: a comparison of **ropivacaine** and **bupivacaine**" Anesthesiology 89:1199-1208, 1998; Kohane et al. "A re-examination of tetrodotoxin for prolonged anesthesia" Anesthesiology 89:119-131, 1998; each of which is. . .

DETD . . . fiberoptic bronchoscopy" Eur. Respir. J 5:1123-1125, 1992; incorporated herein by reference), including the management of asthma (Decco et al. "Nebulized **lidocaine** in the treatment of severe asthma in children: a pilot study" Ann. Allergy Asthma Immunol. 82:29-32, 1999; Hunt et al. "Effect of nebulized **lidocaine** on severe glucocorticoid-dependent asthma" Mayo Clin. Proc. 71:361-368, 1996; incorporated herein by reference). Nebulized **lidocaine** results in lower serum levels of drug than are achieved by equieffective intravenous doses (Groeben et al. "Both intravenous and inhaled **lidocaine** attenuate reflex bronchoconstriction but at different plasma concentrations" Am. J. Respir. Crit. Care Med. 159:530-535, 1999; incorporated herein by reference).. . .

DETD [0138] In summary, controlled release of **bupivacaine** using lipid-protein-sugar particles can provide prolonged duration local anesthesia that is as effective (depth and duration of anesthesia) as that. . .

DETD Biocompatibility of Lipid-Protein-Sugar Particles Containing **Bupivacaine** in the Perineurium

DETD . . . made from high molecular weight poly(lactic-co-glycolic) acid (PLGA) (Castillo et al. "Glucocorticoids prolong rat sciatic nerve

blockade in vivo from **bupivacaine** microspheres" Anesthesiology 85:1157-66, 1996; Curley et al. "Prolonged regional nerve blockade. Injectable biodegradable **bupivacaine**/polyester microspheres" Anesthesiology 84:1401-1410, 1996; Drager et al. "Prolonged intercostal nerve blockade in sheep using controlled release **bupivacaine** and dexamethasone from polyester microspheres" Anesthesiology 89: 969-979, 1998; Le Corre et al. "Preparation and characterization of **bupivacaine**-loaded polylactide and polylactide-coglycolide microspheres" Int. J Pharmaceut. 107:41-49, 1994; Le Corre et al. "In vitro controlled release kinetics of local anaesthetics from poly(D,L-lactide) and poly(lactide-co-glycolide) microspheres" J. Microencaps. 14:243-255, 1997; Estebe et al. "Prolongation of spinal anesthesia with **bupivacaine**-loaded (DL-lactide) microspheres" Anesth. Analg. 81:99-103, 1995; Wakiyama et al. "Preparation and evaluation in vitro of polylactic acid microspheres containing local. . . Pharm. Bull. 29:3363-3368, 1981; Wakiyama et al. "Preparation and evaluation in vitro and in vivo of polylactic acid microspheres containing **dibucaine**" Chem. Pharm. Bull. 30:3719-3727, 1982; each of which is incorporated herein by reference), in a blinded study. This comparison is. . . is incorporated herein by reference) when applied perineurally (Drager et al. "Prolonged intercostal nerve blockade in sheep using controlled release **bupivacaine** and dexamethasone from polyester microspheres" Anesthesiology 89: 969-979, 1998; incorporated herein by reference) has been described. As many parameters as. . .

DETD [0143] **Bupivacaine** hydrochloride, human serum albumin (Fraction V), and lactose .beta.-monohydrate were purchased from Sigma Chemical Co. (St. Louis, MO), L-.alpha.-dipalmitoylphosphatidylcholine (DPPC). . . poly (vinyl alcohol) (88% hydrolyzed, MW 20,000) from Polysciences (Warrington, Pa.), and USP grade ethanol from Pharmco Products (Brookfield, Conn.). **Bupivacaine** hydrochloride was made into the free base by alkaline precipitation and filtration.

DETD [0145] LPSPs and PLGA microspheres were prepared and characterized (Kohane et al. "Sciatic nerve blockade with lipid-protein-sugar particles containing **bupivacaine**" Pharm. Res. 2000 (in press); incorporated herein by reference). In brief, LPSP were produced as follows. Dipalmitoylphosphatidyl-choline (DPPC) and **bupivacaine** free base were dissolved in ethanol, and albumin and lactose were dissolved in water. The two solution were mixed (so the final proportion (w/w) of solutes was DPPC 54: albumin 18: lactose 18: **bupivacaine** 10), and spray-dried using a Model 190 bench top spray drier (Buchi Co, Switzerland). PLGA microspheres containing 50% and 0% (w/w) **bupivacaine** were prepared by the single emulsion method using PLGA.sub.110. Polymer and **bupivacaine** free base (200 mg total mass) were dissolved in 1.5 ml methylene chloride, and added to a solution of 1%. . . Co., Newark, N.J.), washed three times with water by centrifugation, then lyophilized to dryness. A separate group of 10% (w/w) **bupivacaine** microspheres were produced with PLGA.sub.20. Twenty milligrams of **bupivacaine** and 180 mg of PLGA.sub.20 were dissolved in 5 ml methylene chloride. The mixture was treated as above except that. . .

DETD . . . via a 20 gauge needle under halothane-oxygen anesthesia as described (Kohane et al. "Sciatic nerve blockade with lipid-protein-sugar particles containing **bupivacaine**" Pharm. Res. 2000 (in press); incorporated herein by reference). In brief, each rat was injected with a suspension of 75. . . of 1% sodium carboxymethyl cellulose, 0.1% Tween 80 (Castillo et al. "Glucocorticoids prolong rat sciatic nerve blockade in vivo from **bupivacaine** microspheres" Anesthesiology 85:1157-66, 1996; Curley et al. "Prolonged regional nerve blockade. Injectable biodegradable **bupivacaine** /polyester microspheres" Anesthesiology 84:1401-1410, 1996; Drager et al. "Prolonged intercostal nerve blockade in sheep using controlled release **bupivacaine** and dexamethasone from polyester microspheres" Anesthesiology 89: 969-979, 1998; each of which is

incorporated herein by reference) after gentle agitation. . .
location of the injected particles) was confirmed by hotplate testing (Kohane et aL "Sciatic nerve blockade with lipid-protein-sugar particles containing **bupivacaine**" Pharm. Res. 2000 (in press); incorporated herein by reference) in all animals, except those injected with blank (no **bupivacaine**) particles.

DETD . . . PLGA.sub.110 microspheres has been described in Example 1 and elsewhere (Kohane et al. "Sciatic nerve blockade with lipid-protein-sugar particles containing **bupivacaine**" Pharm. Res. 2000 (in press); incorporated herein by reference). Relevant aspects are summarized in Table 2, together with data on PLGA.sub.20 microspheres.

TABLE 2

Characteristics of particles

	Composition		
Particle Type	Polymer	**Bupivacaine**.sup.1 % (w/w)	Median particle diameter (.mu.m)
LPSP.sup.2	--.sup.3	10%	4.4 .+-. 0.4
PLGA.sup.4	PLGA.sub.110	50%	59 .+-.. . . 0.2

.sup.1Theoretical loading. Actual loading was approximately 80% of this value (Kohane et al. "Sciatic nerve blockade with lipid-protein-sugar particles containing **bupivacaine**" Pharm. Res. 2000 (in press); incorporated herein by reference).

.sup.2Lipid proteins sugar particles.

.sup.3The excipients are dipalmitoylphosphatidylcholine, albumin, and lactose.. . .

DETD [0164] Groups of rats were injected at the sciatic nerve with 10% (w/w) **bupivacaine** LPSPs or 50% (w/w) PLGA.sub.11o microspheres. The sciatic nerves were removed 4 days (n=4), 2 weeks (n=6), or 7 months. .

DETD . . . rats were injected with PLGA.sub.20 microspheres 3.6.+-.0.2 .mu.m in diameter (vs. 4.4.+-.0.4 .mu.m for the LPSPs) loaded 10% (w/w) with **bupivacaine**. (In order to further minimize the dwell time of the microspheres we used PLGA.sub.20, a polymer that has a much. .

DETD . . . equivalent durations of sciatic sensory nerve blockade in the rat (Kohane et al. "Sciatic nerve blockade with lipid-protein-sugar particles containing **bupivacaine**" Pharm. Res. 2000 (in press); incorporated herein by reference).

DETD . . . was consistent with the observations of other investigators (Drager et al. "Prolonged intercostal nerve blockade in sheep using controlled release **bupivacaine** and dexamethasone from polyester microspheres" Anesthesiology 89: 969-979, 1998; van der Elst et al. "Bone tissue response to biodegradable polymers. . .

DETD [0183] It bears mentioning that the tissue reaction to both particle types was not due to the encapsulated **bupivacaine**. Blank (no drug) LPSPs and PLGA.sub.110 microspheres (n=4 each) produced the same qualitative and quantitative tissue effects seen with drug-loaded. . .

DETD . . . to free muscimol in an in vitro dialysis assay as described above in the section, entitled "In vitro release of **bupivacaine** from microparticles," of Example 1. LPSPs were also prepared containing 20% (w/w) of diphenylhydantoin.

CLM What is claimed is:

1. A pharmaceutical **composition** comprising microparticles of an agent encapsulated in a matrix comprising lipid, protein, and sugar.

2. A pharmaceutical **composition** comprising microparticles of an agent encapsulated in a matrix, wherein the matrix comprises at least three components selected from the. . .

3. A pharmaceutical **composition** comprising microparticles of

an agent encapsulated in a matrix, wherein the matrix comprises at least two components selected from the. . .

4. A pharmaceutical **composition** comprising microparticles of an agent encapsulated in a matrix comprising lipid and protein.

5. A pharmaceutical **composition** comprising microparticles of an agent encapsulated in a matrix comprising lipid and sugar.

6. A pharmaceutical **composition** comprising microparticles of an agent encapsulated in a matrix comprising protein and sugar.

7. The pharmaceutical **composition** of claim 1 wherein the agent is a therapeutic agent.

8. The pharmaceutical **composition** of claim 1 wherein the agent is a local anesthetic.

9. The pharmaceutical **composition** of claim 1 wherein the agent is selected from the group consisting of **procaine**, **lidocaine**, **dibucaine**, **tetracaine**, **bupivacaine**, **mepivacaine**, and **articaine**.

10. The pharmaceutical **composition** of claim 1 wherein the agent is **bupivacaine**.

11. The pharmaceutical **composition** of claim 1 wherein the agent is an anticonvulsant.

12. The pharmaceutical **composition** of claim 1 wherein the agent is a vasodilator.

13. The pharmaceutical **composition** of claim 1 wherein the agent is a protein.

14. The pharmaceutical **composition** of claim 1 wherein the agent is a lipid.

15. The pharmaceutical **composition** of claim 1 wherein the agent is a glycosaminoglycan.

16. The pharmaceutical **composition** of claim 1 wherein the agent is a diagnostic agent.

17. The pharmaceutical **composition** of claim 1 wherein the agent is a prophylactic agent.

18. The pharmaceutical **composition** of claim 1 wherein the lipid is a naturally occurring lipid.

19. The pharmaceutical **composition** of claim 1 wherein the lipid is an emulsifier.

20. The pharmaceutical **composition** of claim 1 wherein the lipid is a surfactant.

21. The pharmaceutical **composition** of claim 1 wherein the lipid is positively charged.

22. The pharmaceutical **composition** of claim 1 wherein the lipid is negatively charged.

23. The pharmaceutical **composition** of claim 1 wherein the lipid has no charge.

24. The pharmaceutical **composition** of claim 1 wherein the lipid is a phosphatidylcholine.

25. The pharmaceutical **composition** of claim 1 wherein the lipid is dipalmitoylphosphatidylcholine (DPPC).

26. The pharmaceutical **composition** of claim 1 wherein the lipid is polyvinyl alcohol.

27. The pharmaceutical **composition** of claim 1 wherein the lipid is a phospholipid.

28. The pharmaceutical **composition** of claim 1 wherein the lipid is selected from the groups consisting of phosphoglycerides; phosphatidylcholines; dipalmitoyl phosphatidylcholine (DPPC); dioleylphosphatidyl ethanolamine. . .

29. The pharmaceutical **composition** of claim 1 wherein the lipid is a derivatized lipid.

30. The pharmaceutical **composition** of claim 1 wherein the protein is an albumin.

31. The pharmaceutical **composition** of claim 1 wherein the protein is a whole cell extract.

32. The pharmaceutical **composition** of claim 1 wherein the protein is an antibody.

33. The pharmaceutical **composition** of claim 1 wherein the protein is an enzyme.

34. The pharnacuetical **composition** of claim 1 wherein the protein is glucose oxidase.

35. The pharmaceutical **composition** of claim 1 wherein the protein is insulin.

36. The pharmaceutical **composition** of claim 1 wherein the sugar comprises a mixture of complex and simple sugars.

37. The pharmaceutical **composition** of claim 1 wherein the sugar is lactose.

38. The pharmaceutical **composition** of claim 1 wherein the sugar is cellulose.

39. The pharmaceutical **composition** of claim 1 wherein the sugar is a chemically modified sugar.

40. The pharmaceutical **composition** of claim 1 wherein the sugar is a glycosaminoglycan.

41. The pharmaceutical **composition** of claim 1 wherein the sugar is dextran.

42. The pharmaceutical **composition** of claim 1 wherein the sugar is a chemically modified dextran.

43. The pharmaceutical **composition** of claim 1 wherein the sugar is chondroitin sulfate.

44. The pharmaceutical **composition** of claim 1 wherein the sugar is a derivatized sugar.

45. The pharmaceutical **composition** of claim 1 wherein the sugar is a chemically modified sugar.

47. The pharmaceutical **composition** of claim 1 wherein the ratio of lipid to protein to sugar is approximately 3:1:1.

48. The pharmaceutical **composition** of claim 1 wherein the lipid comprises 0-99% of the matrix by weight.

49. The pharmaceutical **composition** of claim 1 wherein the lipid comprises 3-99% of the matrix by weight.

50. The pharmaceutical **composition** of claim 1 wherein the lipid comprises 20-60% of the matrix by weight.

51. The pharmaceutical **composition** of claim 1 wherein the protein comprises 0-95% of the matrix by weight.

52. The pharmaceutical **composition** of claim 1 wherein the protein comprises 10-30% of the matrix by weight.

53. The pharmaceutical **composition** of claim 1 wherein the protein comprises 1-20% of the matrix by weight.

54. The pharmaceutical **composition** of claim 1 wherein the sugar comprises 0-60% of the matrix by weight.

55. The pharmaceutical **composition** of claim 1 wherein the sugar comprises 0.5%-50% of the matrix by weight.

56. The pharmaceutical **composition** of claim 1 wherein the sugar comprises 10-30% of the matrix by weight.

57. The pharmaceutical **composition** of claim 1 wherein the microparticles are less than 50 micrometers in diameter.

58. The pharmaceutical **composition** of claim 1 wherein the microparticles are less than 10 micrometers in diameter.

59. The pharmaceutical **composition** of claim 1 wherein the microparticles are less than 5 micrometers in diameter.

60. The pharmaceutical **composition** of claim 1 wherein the microparticles are less than 1 micrometer in diameter.

61. The pharmaceutical **composition** of claim 1 wherein the microparticles are less than 500 manometers in diameter.

72. The method of claim 66 wherein the local anesthetic is **bupivacaine**.

L16 ANSWER 3 OF 50 USPATFULL

ACCESSION NUMBER:	2002:243798 USPATFULL
TITLE:	Reagent system and method for increasing the luminescence of lanthanide(III) macrocyclic complexes
INVENTOR(S):	Leif, Robert C., San Diego, CA, UNITED STATES Vallarino, Lidia, Richmond, VA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002132992	A1	20020919
APPLICATION INFO.:	US 2001-10597	A1	20011206 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2000-484670, filed on 18		

Jan 2000, GRANTED, Pat. No. US 6340744

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-116316P	19990119 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Gary M. Nath, Nath & Associates PLLC, Sixth Floor, 1030 Fifteenth Street, NW, Washington, DC, 20005-1503
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 2097
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are a spectrofluorimetrically detectable luminescent **composition** and processes for enhancing the luminescence of one or more lanthanide-containing macrocycles. The luminescent **composition** comprises a micelle-producing amount of at least one surfactant, at least one energy transfer acceptor lanthanide element macrocycle compound having. . . samarium, and terbium macrocyclic complexes, which were taught in our U.S. Pat. No. 5,696,240. The enhanced luminescence afforded by the **composition** enables the detection and/or quantitation of many analytes in low concentrations without the use of expensive, complicated time-gated detection systems.

SUMM [0011] In accordance with this invention, there is provided a spectrofluorimetrically detectable luminescent **composition** comprising water, a micelle-producing amount of at least one surfactant, at least 1.times.10.sup.-10 moles/liter of at least one energy transfer. . .

SUMM . . . invention occurs as very narrow emission peaks in the red. This difference allows the major emission of the enhanced luminescence **composition** of this invention to be unambiguously detected even when its intensity is much lower than that of the very strong. . .

SUMM [0024] It is a further feature of the invention that the **composition** and method of the invention not only provide enhanced luminescence but also minimize the interfering effect of non-specific binding of. . .

SUMM [0025] The lanthanide energy transfer acceptor macrocyclic compound ingredient of the **composition** of the invention is characterized by kinetic stability even in very dilute aqueous solution. The compound is resistant to removal. . .

SUMM [0026] The lanthanide energy transfer acceptor macrocyclic compound ingredient of the **composition** of the invention is further characterized by the fluorescence spectrum with emission in the range from 500 to 950 nanometers. . .

SUMM [0048] In a particularly preferred embodiment, a **composition** of the invention can include two different MMac each coupled to a polynucleotide as energy transfer acceptors, or two different. . .

SUMM [0054] As a result of the ability of analytes including reactive biomolecules to bond to a functionalized macrocycle in a **composition** of this invention, as expressed by Z in Formula V, the enhanced luminescence of the **composition** can serve as an analytical tool for estimating such biomolecules as analytes. Thus the analyte can be any compound of. . .

SUMM [0059] (i) aminoacid derived hormones including thyroxine, **epinephrine**,

SUMM [0067] (e) drugs of abuse including **cocaine**, tetrahydrocannabinol,

SUMM [0084] (xii) toxins including cholera toxin, diphtheria toxin, and **botulinum** toxin, snake venom toxins, tetrodotoxin, saxitoxin,

SUMM . . . lanthanide element of the energy transfer acceptor macrocyclic compound is europium, samarium, or terbium. In a particularly preferred embodiment, a **composition** of the invention includes an energy transfer acceptor macrocyclic compound in which the central atom is

europium and a second. . . As a result, two different biomolecules can be measured in the presence of one another by using an enhanced luminescence **composition** of the invention whereby one is coupled to a functionalized europium macrocycle and another is coupled to a functionalized samarium. . .

SUMM [0092] Also in accordance with this invention, the enhanced luminescence of the **composition** of the invention is produced by the interaction in an aqueous micelle organization of an energy transfer acceptor lanthanide element. . .

SUMM [0093] The energy transfer donor compound in the **composition** is present in a concentration greater than the concentration of the energy transfer acceptor macrocycle compound. The concentration of the. . .

SUMM [0094] In a preferred **composition** according to the invention, the energy transfer donor compound is an ionic compound of or complex of gadolinium (III). The. . .

SUMM [0095] The enhanced luminescence **composition** of the invention is preferably adjusted to a pH in the range from 5.5 to 8.5, suitably by use of. . .

SUMM [0096] The enhanced luminescence **composition** of the invention exists in a micellar organization. The importance of micellar organization to the enhanced luminescence **composition** is demonstrated by the observation that a water-miscible polar solvent such as ethanol when added to the characteristically cloudy and luminous **composition** completely discharges the luminescence and simultaneously turns the cloudy micellar liquid clear. Once formed in an aqueous micellar organization, the **composition** of the invention can be transferred to an immiscible non-aqueous medium and/or dried, as by evaporation or lyophilization, with preservation of its luminescence. To provide the micellar organization, the **composition** includes a micelle-forming amount of a surfactant.

SUMM . . . concentration of a surfactant whose CMC is not known is readily determined by incremental addition of the surfactant to a **composition** containing all the other intended ingredients until enhanced luminescence is observed.

SUMM . . . In addition to the above disclosed energy transfer acceptor macrocycle compound, energy transfer donor compound, surfactant, and buffer ingredients, the **composition** of the invention can also contain one or more synergistic ligands to increase the luminescence of the **composition** beyond that attainable in absence of synergistic ligand. Such ligands do not displace the macrocycle of the acceptor or release. . .

SUMM [0103] Moreover, the **composition** of the invention can contain one or more betadiketones. The concentration of betadiketone when present can range from 1.times.10.sup.-2 to. . .

SUMM [0132] In an important extension of the method of the invention, the enhanced fluorescence **composition** of the invention formed in an aqueous micellar organization can be dried and/or transferred into a non-aqueous medium and measured. . .

DETD [0178] The concentrations of EuMac was varied as appropriate, while the **composition** of the solution was kept constant. The emission spectra of solutions were obtained with a SPEX 1692T spectrofluorometer. The slits. . .

CLM What is claimed is:

. . . (b) Hormones and related compounds including (i) steroid hormones including estrogen, corticosterone, testosterone, ecdysone, (ii) aminoacid derived hormones including thyroxine, **epinephrine**, (iii) prostaglandins, (iv) peptide hormones including oxytocin, somatostatin, (c) pharmaceuticals including aspirin, penicillin, hydrochlorothiazide, (d) Nucleic acid constituents including (i). . . mono, di, and triphosphates of 2-deoxyadenosine, 2-deoxycytidine, 2-deoxythymidine, 2-deoxyguanosine, 5-bromo-2-deoxyuridine, adenosine, cytidine, uridine, guanosine, 5-bromouridine, (e) drugs of abuse including **cocaine**, tetrahydrocannabinol, (f) histological

stains including fluorescein, DAPI (g) pesticides including digitoxin, (h) and miscellaneous haptens including diphenylhydantoin, quinidine, RDX.

. . . annexin V, bak, bcl-2, fas caspases, nuclear matrix protein, cytochrome c, nucleosome, (xii) toxins including cholera toxin, diphtheria toxin, and **botulinum** toxin, snake venom toxins, tetrodotoxin, saxitoxin, (xiii) lectins including concanavalin, wheat germ agglutinin, soy bean agglutinin, (b) polysialic acids including.

. .

18. A spectrophotometrically detectable luminescent **composition** comprising water, a micelle-producing amount of at least one surfactant, at least 1.times.10.sup.-10 moles/liter of at least one energy transfer.

. .

19. The **composition** of claim 18, wherein said energy acceptor lanthanide element functionalized complex is a macrocycle.

20. The **composition** of claim 19, wherein said macrocycle contains at least nine ring atoms of which at least three are donor atoms.

. . .

21. A **composition** according to claim 19, in which the lanthanide macrocycle has eighteen ring members.

22. A **composition** according to claim 18 which is a cloudy solution.

23. The **composition** resulting from the transfer of a **composition** of claim 18 to a non-aqueous environment.

24. The **composition** resulting from the transfer of a **composition** of claim 18 to a non-aqueous environment and removal of water.

L16 ANSWER 4 OF 50 USPATFULL

ACCESSION NUMBER:	2002:144126 USPATFULL
TITLE:	Assay method utilizing induced luminescence
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Kirakossian, Hrair, San Jose, CA, United States Pease, John S., Los Altos, CA, United States Daniloff, Yuri, Mountain View, CA, United States Wagner, Daniel B., Sunnyvale, CA, United States
PATENT ASSIGNEE(S):	Dade Behring Marburg GmbH, Marburg, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6406913	B1	20020618
APPLICATION INFO.:	US 1995-471130		19950606 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1991-704569, filed on 22 May 1991, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Smith, Lynette R. F.		
ASSISTANT EXAMINER:	Hines, Ja-Na		
LEGAL REPRESENTATIVE:	Finnegan, Henderson, Farabow, Garrett & Dunner L.L.P.		
NUMBER OF CLAIMS:	93		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	8 Drawing Figure(s); 4 Drawing Page(s)		
LINE COUNT:	3429		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . comprising a suspendible particle having incorporated therein a chemiluminescent compound where the particle has an sbp member bound

thereto. The **composition** can further comprise a suspendible particle having a photosensitizer incorporated therein.

SUMM Another embodiment of the invention concerns kits comprising in packaged combination a **composition** that includes (1) a suspendible particle having a chemiluminescent compound where the particle has an sbp member bound thereto, and (2) a photosensitizer. The kit can further include a **composition** comprising a second suspendible particle comprising a photosensitizer where the particle has an sbp member bound thereto.

DETD In one aspect of the present invention a **composition** comprising a photosensitizer and a ligand, receptor or polynucleotide binds in an assay to a **composition** comprising a chemiluminescent compound and a ligand, receptor or polynucleotide. The chemiluminescent compound can react with singlet oxygen and the. . . the photosensitizer usually by irradiation of the photosensitizer. Singlet oxygen produced by the photosensitizer that is not bound to the **composition** comprising a chemiluminescent compound is unable to reach the chemiluminescent compound before undergoing decay (t.sub.1/2 is about two microseconds in water). The **composition** comprising a photosensitizer that becomes bound to the **composition** comprising the chemiluminescent compound produces singlet oxygen that reacts with the chemiluminescent compound because such singlet oxygen can survive the. . . has a much longer lifetime, namely, greater than about one hundred microseconds. The analyte must modulate the binding between the **composition** comprising the photosensitizer and the **composition** comprising the chemiluminescent compound. Usually, at least one of the chemiluminescent compound and the photosensitizer is associated with a surface,. . .

DETD Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

DETD . . . Spore-forming Bacilli Phialophora jeanselmei
Bacillus anthracis Microsporum gypseum
Bacillus subtilis Trichophyton mentagrophytes
Bacillus megaterium Keratinomyces ajelloi
Bacillus cereus Microsporum canis
Anaerobic Spore-forming Bacilli Trichophyton rubrum
Clostridium **botulinum** Microsporum adouini
Clostridium tetani Viruses
Clostridium perfringens Adenoviruses
Clostridium novyi Herpes Viruses
Clostridium septicum Herpes simplex
Clostridium histolyticum Varicella (Chicken pox)
Clostridium tertium Herpes Zoster (Shingles)
Clostridium. . .

DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD Receptor ("antiligand")--any compound or **composition** capable

of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD . . . both compounds to associate with the same particle. This possibly can be further reduced by utilizing particles of only one **composition** that are associated with either the photosensitizer or chemiluminescent compound or by using two types of particles that differ in **composition** so as to favor association of the photosensitizer with one type of particle and association of the chemiluminescent compound with. . .

DETD . . . combined in one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises (1) a **composition** comprising a suspendible particle comprising a chemiluminescent compound, the particle having an sbp member bound to it, and (2) a. . .

CLM What is claimed is:

. . . (a) combining either simultaneously or wholly or partially sequentially (1) said medium suspected of containing said analyte, (2) a first **composition** comprising a member of a specific binding pair (sbp) member associated to a photosensitizer and a suspendible particle, and (3) a second **composition** comprising an sbp member associated to a chemiluminescent compound and a suspendible particle; (b) forming a complex comprising said first **composition**, said second **composition**, and said analyte, wherein said analyte brings said photosensitizer and said chemiluminescent compound into close proximity in said complex; (c). . .

14. The method of claim 6, wherein the second **composition** comprises further a fluorescent energy acceptor.

. . . (a) combining either simultaneously or wholly or partially sequentially (1) said medium suspected of containing said protein, (2) a first **composition** comprising an antibody as a member of a specific binding pair (sbp) associated to a phthalocyanine photosensitizer and a suspendible latex particle, and (3) a second **composition** comprising an antibody as a sbp member associated to an enol ether chemiluminescent compound and a suspendible latex particle; (b) forming a complex comprising said first **composition**, said second **composition**, and said protein, wherein said protein brings said photosensitizer and said chemiluminescent compound into close proximity in said complex; (c). . .

32. The method of claim 24, wherein the second **composition** comprises further a fluorescent energy acceptor.

41. The method of claim 40, wherein said **composition** is treated by irradiation to excite said photosensitizer.

42. The method of claim 41, wherein said **composition** is irradiated with light having a wavelength of 450-950 nm.

. . . analyte in a sample suspected of containing said analyte, said method comprising: (a) providing a medium comprising: (1) a first **composition** comprising a photosensitizer, a first specific binding pair (sbp) member, and a support for the photosensitizer and the first sbp member; (2) a second **composition** comprising a chemiluminescent compound, a second sbp member that binds with the first sbp member, and a support for the. . . chemiluminescent compound and the second sbp member; and (3) said sample suspected of containing said analyte; wherein either said first **composition**, or said second **composition**, or both of said first **composition** and said second **composition** are suspendible in said medium; (b) treating said medium with energy or a reactive compound to form singlet oxygen from. . . said photosensitizer, wherein said singlet oxygen

diffuses in said medium; wherein said analyte, if present, either (i) brings said second **composition** into close proximity to said first **composition**, or (ii) blocks said second **composition** from coming into close proximity to said first **composition**; and (c) detecting a signal produced by said chemiluminescent compound after singlet oxygen has reacted with said chemiluminescent compound; wherein. . .

L16 ANSWER 5 OF 50 USPATFULL

ACCESSION NUMBER:	2002:141535 USPATFULL
TITLE:	Compositions and methods for the treatment of anorectal disorders
INVENTOR(S):	Parks, Thomas P., San Mateo, CA, UNITED STATES Mak, Vivien, Palo Alto, CA, UNITED STATES Lee, Jung-Chung, Sunnyvale, CA, UNITED STATES Lee, Charles, Union City, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002072522	A1	20020613
APPLICATION INFO.:	US 2001-919590	A1	20010730 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-460306, filed on 13 Dec 1999, PENDING Continuation-in-part of Ser. No. US 2000-595390, filed on 14 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2001-769621, filed on 23 Jan 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-222267P	20000731 (60)
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DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS:	34
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	13 Drawing Page(s)
LINE COUNT:	2514

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Eur J. Gastroenterology 9(5):442-6 (1997); Pitt, J. et al., Dis Colon Rectum 43(6)800-803 (2000)). Conversely, the .alpha.-receptor agonists methoxamine and **phenylephrine** increase anal pressure (Speakman, C. T. 1997 supra; Carapeti, E. A. et al., Br J Surg 86(2):267-70 (1999)). Low anal. . . relaxant effects of the .beta.-adrenergic agonist isoproterenol than control tissues, whereas no differences were noted in the contractile responses to **phenylephrine** and potassium chloride (a membrane depolarizing agent). However, it remains to be determined whether .beta.-adrenergic agonists offer disease-specific advantages for. . .

SUMM [0031] In yet another aspect, the present invention provides a **composition** for the treatment of anorectal disorders comprising a methylxanthine compound. In preferred embodiments, the compound is theophylline or dyphylline. In. . .

DETD [0092] The term "pharmaceutical **composition**" means a **composition** suitable for pharmaceutical use in a subject, including an animal or human. A pharmaceutical **composition** generally comprises an effective amount of an active agent and a pharmaceutically acceptable carrier.

DETD . . . about 0.01 to about 10 percent by weight. All weight percentages herein are based on the total weight of the **composition**. For NTG, preferred concentrations are in the range

of from about 0.01 to about 5 percent by weight.

DETD [0107] In one group of embodiments, the **composition** contains an agent which is a phosphodiesterase (PDE) inhibitor. Inhibitors of phosphodiesterases (PDE), are agents which can block the breakdown. . .

DETD [0109] In another group of embodiments, the **composition** contains an agent which is a phosphodiesterase type II (PDE II) inhibitor. Suitable phosphodiesterase type II inhibitors include EHNA.

DETD [0110] In yet another group of embodiments, the **composition** contains an agent which is a phosphodiesterase type IV (PDE IV) inhibitor. Suitable phosphodiesterase type IV inhibitors include ariflo (SB207499),. . .

DETD [0111] In still another group of embodiments, the **composition** contains an agent which is a dual selective phosphodiesterase inhibitor, preferably a PDE III/IV inhibitor such as, for example, zardaverine.

DETD [0112] In yet another group of embodiments, the **composition** contains an agent which is a nonspecific phosphodiesterase (nonspecific PDE) inhibitor. Suitable nonspecific phosphodiesterase inhibitors include IBMX, theophylline, dyphylline theobromine,. . .

DETD [0113] In still another group of embodiments, the **composition** contains an agent which is a superoxide anion (O.sub.2.sup.-) scavenger. Superoxide can react with NO and dramatically reduce its biological. . .

DETD [0114] In yet another group of embodiments, the **composition** contains an agent which is a .beta.-adrenergic agonist, preferably a .beta..sub.2- or .beta..sub.3-adrenergic receptor agonist. A variety of .beta.-adrenergic agonists. . .

DETD [0116] In yet another group of embodiments, the **composition** contains an agent which is an estrogen or estrogen analog or mimetic. As used herein, the term "estrogens" is meant. . .

DETD [0117] In yet another group of embodiments, the **composition** contains an agent which is an .alpha..sub.1-adrenergic antagonist. The sympathetic neurotransmitter norepinephrine contracts sphincter smooth muscle via .alpha..sub.1-adrenergic receptors. Pharmacological. . . inhibitors (e.g. .alpha.-methyl tyrosine), and agents which destroy sympathetic nerve terminals (e.g. 6-hydroxy dopamine). Accordingly, in a related embodiment, the **composition** contains an alternative sympatholytic agent, such as an .alpha..sub.2-adrenergic receptor agonist, a nerve terminal norepinephrine depleting agent, a norepinephrine synthesis. . .

DETD [0133] In one group of embodiments, the **composition** contains a suitable .beta.-adrenergic receptor agonist and a pharmaceutically acceptable carrier, preferably one formulated for local delivery to the site. . .

DETD [0134] In another group of embodiments, the **composition** contains another agent selected from cAMP-hydrolyzing PDE inhibitors (e.g., a PDE IV inhibitor), nonspecific PDE inhibitors, .alpha..sub.1-adrenergic antagonists, adenosine receptor. . .

DETD [0145] In some embodiments, the **composition** comprises an additional agent which is a cAMP-dependent protein kinase activator, an estrogen or estrogen like compound, an .alpha..sub.1-adrenergic antagonist,. . .

DETD . . . sphincters, including the internal anal sphincter, lower esophageal sphincter, pyloric sphincter, sphincter of Oddi, and the ileocolic sphincter. The topical **composition** is also useful in treating conditions resulting from spasms and/or hypertonicity of sphincters of the anorectal region including anal fissure,. . .

DETD . . . agonist, L-type calcium channel blocker, .alpha.-adrenergic antagonist, ATP-sensitive potassium channel activator, sympathetic nerve terminal destroyer, estrogen or estrogen-like compound or **botulinum** toxin in combination with a pharmaceutically acceptable carrier and at least one of the following second pharmacologic agents: a local anesthetic (e.g., **lidocaine**, **prilocaine**, etc.), local anti-inflammatory agent (e.g.,

naproxen, pramoxicam, etc.), corticosteroid (e.g., cortisone, hydrocortisone, etc.), anti-itch agent (e.g., loperamide diphylenoxalate, etc.), an. . . agent that promotes local tissue sclerosis (e.g., alum, etc.), or menthol. The first pharmacologic agent is typically present in the **composition** in unit dosage form effective for treatment of a first medical condition(s), such as an anal disease or pain associated with an anal disease. The second pharmacologic agent is typically present in the **composition** in unit dosage form effective for treatment of a second medical condition(s), or a condition(s), symptom(s) or effect(s) associated with. . .

DETD . . . present in compositions of the invention in an amount of from about 0.001% to about 15% by weight of the **composition**. In another aspect, the active agent is present in an amount of from about 0.01% to about 7.5% by weight, more preferably from about 0.05% to about 2% by weight of the **composition**.

DETD . . . matrix or agent-polymer matrix is then dispersed in a hydrophilic vehicle to form a semi-solid. After administration of such hydrophilic **composition** into the appropriate anal area, such as the anal canal or anal sphincter, the water in the semi-solid preparation is. . .

DETD . . . hydrophobic compositions and preparations. Plastibase is a mineral oil base that only partially dissolves the nitric oxide donor. The semi-solid **composition** forms a thin coating on the anal region to which the **composition** has been applied (such as the anal canal or anal sphincter area) and slowly releases the active. The prolonged action. . .

DETD . . . be produced in a metered dose inhaler or nebulizer, or in a mist sprayer. Aerosol also includes a dry powder **composition** of a compound of the pharmacological agent suspended in air or other carrier gas, which may be delivered by insufflation. . .

DETD [0205] The present invention further provides methods of using the compositions above in combination with local anesthetic agents, for example **lidocaine**, **prilocaine**, etc. Each of the compositions will typically be in a pharmaceutically acceptable dosage form as an effective treatment for a. . . In another aspect, the present invention provides methods for treating anal disorders which comprise administering an effective amount of such **composition** along with a local anesthetic agent to a subject in need of such treatment. Such compositions can be administered orally,. . .

DETD . . . In another aspect, the present invention provides methods for treating anal disorders which comprise administering an effective amount of such **composition** along with a local anesthetic agent to a subject in need of such treatment. Such compositions can be administered orally,. . .

DETD . . . Gut 10(8): 674-7 (1969)). Recent clinical trials using one of the most potent toxins known, botulinus toxin, produced by Clostridium **botulinum**, have demonstrated success in healing anal fissures after multiple injections of the toxin directly into the IAS. Botulinus toxin presumably. . .

DETD [0300] A **composition** of a base gel comprising 1.0 gm of salbutamol, 0.6 gm of carbopol 1342 USP, 35.44 gm of propylene glycol,. . .

DETD [0301] One example of a topical **composition** comprises 0.05 to 1% sildenafil, 75% (w/w) white petrolatum USP, 4% (w/w) paraffin wax USP/NF, lanolin 14% (w/w), 2% sorbitan. . .

DETD [0302] Yet another example of a topical **composition** comprises nitroglycerin at 0.1% concentration and sildenafil at 0.1% concentration can be incorporated in the same ointment base as mentioned above. This **composition** can be applied topically from a metered dosing device where a 50 mg to 1.5 gm dose of the **composition** is administered to the afflicted anorectal tissue to achieve the desired therapeutic effects.

DETD [0304] A **composition** of aminothylline topical spray

composition comprises 0.1 to 5.0% (w/w) of aminothylline, acetylated lanolin alcohol, aloe vera, butane, cetyl acetate, hydrofluorocarbon, methyl paraben, PEG-8 laurate. . . inhibitor can vary between 0.5% to 5%. Other non-hydrofluorocarbon propellant can also be used instead of hydrofluorocarbon in the current **composition** . This **composition** can be sprayed directly onto the afflicted tissue once to four times daily to achieve the desired relief of signs and/or symptoms associated with anorectal disorders. This **composition** can also include menthol and **benzocaine** to provide the immediate local pain relief and soothing sensation whereas aminophylline provides the longer lasting relaxation of anal sphincter. . .

DETD [0305] A base cream **composition** comprises 2 gm prazosin hydrochloride (2.0% w/w), 54.3 gm of purified water USP, 2 gm of Sepigel 305, 4.5 gm. . .

DETD . . . from a topical spray to patients diagnosed with hemorrhoidal disorders, alone or in combination with a local anesthetic, for example, **lidocaine**, or in combination with a mixed .beta..sub.2- and .beta..sub.3-adrenergic agonist, for example salbutamol, or in combination with a PDE IV. . .

CLM What is claimed is:

1. A **composition** for the treatment of an anorectal disorder, and for controlling the pain associated therewith, said **composition** comprising at least one internal anal sphincter relaxing agent selected from the group consisting of NO donors, phosphodiesterase type II. . .

2. A **composition** in accordance with claim 1, wherein said **composition** comprises a first agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and. . .

3. A **composition** in accordance with claim 1, wherein said carrier is formulated for local application.

4. A **composition** according to claim 1, wherein said **composition** comprises a first relaxing agent that is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO. . .

5. A **composition** according to claim 4, wherein said .beta..sub.2-adrenergic agonist is salbutamol or terbutaline.

6. A **composition** in accordance with claim 1, wherein said **composition** comprises a first relaxing agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO. . .

7. A **composition** in accordance with claim 6, wherein said second agent is minoxidil or diazoxide.

8. A **composition** in accordance with claim 1, wherein said **composition** comprises a first relaxing agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO. . .

9. A **composition** in accordance with claim 8, wherein said second agent is theophylline or dyphylline.

10. A **composition** according to claim 1, comprising an adenosine receptor antagonist.

11. A **composition** according to claim 10, wherein said antagonist is theophylline or dyphylline.

12. A **composition** according to claim 1, comprising a ATP sensitive K.sup.+ channel opener.

13. A **composition** according to claim 12, wherein said opener

is minoxidil or diazoxide.

14. A **composition** according to claim 1, wherein said **composition** comprises a .beta..sub.2-adrenergic agonist.

15. A **composition** according to claim 14, wherein said .beta..sub.2-adrenergic agonist is salbutamol or terbutaline.

. . . associated therewith, the method comprising administering to a subject in need of such treatment a therapeutically effective amount of a **composition** that comprises at least one internal anal sphincter relaxing agent selected from the group consisting of NO donors, phosphodiesterase type. . .
17. A method in accordance with claim 16, wherein said **composition** comprises a first agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and. . .
19. A method according to claim 16, wherein said **composition** comprises a first relaxing agent that is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO. . .
21. A method in accordance with claim 16, wherein said **composition** comprises a first relaxing agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO. . .
23. A method in accordance with claim 16, wherein said **composition** comprises a first relaxing agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO. . .
25. A method according to claim 16, wherein said **composition** comprises an adenosine receptor antagonist.

27. A method according to claim 16, wherein said **composition** comprises a ATP sensitive K.sup.+ channel opener.

29. A method according to claim 16, wherein said **composition** comprises a .beta..sub.2-adrenergic agonist.

32. A method of claim 16, wherein said **composition** comprises a terbutaline or salbutamol.

33. A method of claim 16, wherein said **composition** comprises theophylline or diphylline.

34. A method of claim 16, wherein said **composition** comprises minoxidil or diazoxide.

L16 ANSWER 6 OF 50 USPATFULL

ACCESSION NUMBER:	2002:14058 USPATFULL		
TITLE:	Reagent system and method for increasing the luminescence of lanthanide(III) macrocyclic complexes		
INVENTOR(S):	Leif, Robert C., 5648 Toyon Rd., San Diego, CA, United States 92115-1022 Vallarino, Lidia, 1009 West Ave, Richmond, VA, United States 23220		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6340744	B1	20020122
APPLICATION INFO.:	US 2000-484670		20000118 (9)
	NUMBER		DATE
PRIORITY INFORMATION:	US 1999-116316P		19990119 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Hartley, Michael G.
LEGAL REPRESENTATIVE: Schwartz, Robert M., Kauder, Otto S., Hibnick, Gerald R.
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 2136
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are a spectrofluorimetrically detectable luminescent **composition** and processes for enhancing the luminescence of one or more lanthanide-containing macrocycles. The luminescent **composition** comprises a micelle-producing amount of at least one surfactant, at least one energy transfer acceptor lanthanide element macrocycle compound having. . . samarium, and terbium macrocyclic complexes, which were taught in our U.S. Pat. No. 5,696,240. The enhanced luminescence afforded by the **composition** enables the detection and/or quantitation of many analytes in low concentrations without the use of expensive, complicated time-gated detection systems.

SUMM In accordance with this invention, there is provided a spectrofluorimetrically detectable luminescent **composition** comprising water, a micelle-producing amount of at least one surfactant, at least 1.times.10.sup.10 moles/liter of at least one energy transfer. . .

SUMM . . . invention occurs as very narrow emission peaks in the red. This difference allows the major emission of the enhanced luminescence **composition** of this invention to be unambiguously detected even when its intensity is much lower than that of the very strong. . .

SUMM It is a further feature of the invention that the **composition** and method of the invention not only provide enhanced luminescence but also minimize the interfering effect of non-specific binding of. . .

SUMM The lanthanide energy transfer acceptor macrocyclic compound ingredient of the **composition** of the invention is characterized by kinetic stability even in very dilute aqueous solution. The compound is resistant to removal. . .

SUMM The lanthanide energy transfer acceptor macrocyclic compound ingredient of the **composition** of the invention is further characterized by the fluorescence spectrum with emission in the range from 500 to 950 nanometers. . .

SUMM In a particularly preferred embodiment, a **composition** of the invention can include two different MMac each coupled to a polynucleotide as energy transfer acceptors, or two different. . .

SUMM As a result of the ability of analytes including reactive biomolecules to bond to a functionalized macrocycle in a **composition** of this invention, as expressed by Z in formula II, the enhanced luminescence of the **composition** can serve as an analytical tool for estimating such biomolecules as analytes. Thus the analyte can be any compound of. . .

SUMM (i) aminoacid derived hormones including thyroxine, **epinephrine**,

SUMM (e) drugs of abuse including **cocaine**, tetrahydrocannabinol,

SUMM (xii) toxins including cholera toxin, diphtheria toxin, and **botulinum** toxin, snake venom toxins, tetrodotoxin, saxitoxin,

SUMM . . . lanthanide element of the energy transfer acceptor macro-cyclic compound is europium, samarium, or terbium. In a particularly preferred embodiment, a **composition** of the invention includes an energy transfer acceptor macrocyclic compound in which the central atom is europium and a second. . . As a result, two different biomolecules can be measured in the presence of one another by using an enhanced luminescence **composition** of the invention whereby one is coupled to a fuinctionalized europium macrocycle and another is coupled to a functionalized samarium. . .

SUMM Also in accordance with this invention, the enhanced luminescence of the

composition of the invention is produced by the interaction in an aqueous micelle organization of an energy transfer acceptor lanthanide element. . .

SUMM The energy transfer donor compound in the **composition** is present in a concentration greater than the concentration of the energy transfer acceptor macrocycle compound. The concentration of the. . .

SUMM In a preferred **composition** according to the invention, the energy transfer donor compound is an ionic compound of or complex of gadolinium (III). The. . .

SUMM The enhanced luminescence **composition** of the invention is preferably adjusted to a pH in the range from 5.5 to 8.5, suitably by use of. . .

SUMM The enhanced luminescence **composition** of the invention exists in a micellar organization. The importance of micellar organization to the enhanced luminescence **composition** is demonstrated by the observation that a water-miscible polar solvent such as ethanol when added to the characteristically cloudy and luminous **composition** completely discharges the luminescence and simultaneously turns the cloudy micellar liquid clear. Once formed in an aqueous micellar organization, the **composition** of the invention can be transferred to an immiscible non-aqueous medium and/or dried, as by evaporation or lyophilization, with preservation of its luminescence. To provide the micellar organization, the **composition** includes a micelle-forming amount of a surfactant.

SUMM . . . concentration of a surfactant whose CMC is not known is readily determined by incremental addition of the surfactant to a **composition** containing all the other intended ingredients until enhanced luminescence is observed.

SUMM In addition to the above disclosed energy transfer acceptor macrocycle compound, energy transfer donor compound, surfactant, and buffer ingredients, the **composition** of the invention can also contain one or more synergistic ligands to increase the luminescence of the **composition** beyond that attainable in absence of synergistic ligand. Such ligands do not displace the macrocycle of the acceptor or release. . .

SUMM Moreover, the **composition** of the invention can contain one or more betadiketones. The concentration of betadiketone when present can range from 1.times.10.sup.-2 to. . .

SUMM In an important extension of the method of the invention, the enhanced fluorescence **composition** of the invention formed in an aqueous micellar organization can be dried and/or transferred into a non-aqueous medium and measured. . .

DETD The concentrations of EuMac was varied as appropriate, while the **composition** of the solution was kept constant. The emission spectra of solutions were obtained with a SPEX 1692T spectrofluorometer. The slits. . .

CLM What is claimed is:

1. A spectrofluorimetrically detectable luminescent **composition** comprising water, a micelle-producing amount of at least one surfactant, at least 1.times.10.sup.-10 moles/liter of at least one energy transfer. . .

2. A **composition** according to claim 1 in which at least one surfactant is cationic.

3. A **composition** according to claim 2 in which at least one surfactant is a cetyltrimethylammonium halide.

4. A **composition** according to claim 1 in which at least one surfactant is nonionic.

5. A **composition** according to claim 4 in which at least one surfactant is an ethoxylated alkylphenol having 4-14 ethylene oxide units and. . .

6. A **composition** according to claim 1 in which the lanthanide

macrocycle compound has 4 nitrogen atoms and 2 additional atoms selected from. . .
7. A **composition** according to claim 1 in which the lanthanide macrocycle compound has the formula ##STR11## wherein M is a metal ion. . .
8. A **composition** according to claim 7 in which Y is selected from the group consisting of acetate, carboxylate, sulfonate, halide, nitrate, perchlorate,. . .
9. A **composition** according to claim 7 in which at least one of the substituents A, B, C, and D is selected from. . .
10. A **composition** according to claim 7 in which the lanthanide macrocyclic compound is a conjugate having the formula ##STR12## in which from. . .
11. A **composition** according to claim 1 in which the lanthanide element of the energy transfer acceptor macrocyclic compound is selected from the. . .
12. A **composition** according to claim 11 comprising a first energy transfer acceptor macrocyclic compound in which the lanthanide element is europium and. . .
13. A **composition** according to claim 1 in which the energy transfer donor compound is a compound of gadolinium (III).

14. A **composition** according to claim 13 in which the gadolinium compound is selected from the group consisting of gadolinium halides and gadolinium. . .
15. A **composition** according to claim 14 in which the gadolinium compound is gadolinium trichloride.

16. A **composition** according to claim 1 in which the molar concentration of energy transfer donor compound is from 10 to 100,000 times. . .
17. A **composition** according to claim 1 in which the concentration of energy transfer donor compound is in the range from 5.times.10.sup.-5 moles. . .
18. A **composition** according to claim 1 buffered to a pH in the range from 5.5 to 8.5 with a buffer having a. . .
19. A **composition** according to claim 18 in which the buffer is selected from the group consisting of hexamethylenetetramine and tricine.

20. A **composition** according to claim 1 additionally comprising at least one synergistic ligand.

21. A **composition** according to claim 20 in which the synergistic ligand is selected from the group consisting of 1,10-phenanthroline and trioctylphosphine oxide. . . .
22. A **composition** according to claim 1 additionally comprising at least one beta-dike-tone.

23. A **composition** according to claim 22 in which the beta-diketone has the formula RfCOCH.sub.2COQ in which Rf is a perfluoroalkyl group having. . .
24. A **composition** according to claim 23 in which the beta-diketone is 1,1,1-trifluorcl-4-(2-thienyl)-2,4-butanedione.

25. A **composition** according to claim 7 in which the lanthanide macrocycle compound is a EuMac having the formula ##STR13##

26. A **composition** according to claim 25 in which R is methyl.

27. A **composition** according to claim 7 in which the lanthanide macrocycle compound is a SmMac having the formula ##STR14##

28. A **composition** according to claim 27 in which R is methyl.

29. A **composition** according to claim 7 in which the lanthanide macrocycle compound is a TbMac having the formula ##STR15##

30. A **composition** according to claim 29 in which R is methyl.

31. A **composition** according to claim 10 in which the lanthanide macrocycle compound is a conjugate of a MMac with a protein.

32. A **composition** according to claim 31 in which said protein is an antibody.

33. A **composition** according to claim 31 in which said protein is capable of binding biotin.

34. A **composition** according to claim 33 in which said protein is avidin, streptavidin or a derivative thereof.

35. A **composition** according to claim 10 in which the lanthanide macrocycle compound is a conjugate of a MMac with a polynucleotide.

36. A **composition** according to claim 35 comprising a first lanthanide macrocycle compound conjugated with a polynucleotide and a second lanthanide macrocycle compound. . .
37. A **composition** according to claim 36 in which the first lanthanide macrocycle compound contains europium as energy transfer acceptor.

38. A **composition** according to claim 36 in which the second lanthanide macrocycle compound contains samarium as energy transfer acceptor.

39. A **composition** according to claim 36 in which the first lanthanide macrocycle compound is conjugated with normal DNA and the second lanthanide. . .
40. A **composition** according to claim 39 in which the ratio of suspect DNA to normal DNA is in the range from 500:1. . .

L16 ANSWER 7 OF 50 USPATFULL

ACCESSION NUMBER:	2001:97606 USPATFULL
TITLE:	Assay method utilizing induced luminescence
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Kirakossian, Hrair, San Jose, CA, United States Pease, John S., Los Altos, CA, United States Daniloff, Yuri, Mountain View, CA, United States Wagner, Daniel B., Sunnyvale, CA, United States
PATENT ASSIGNEE(S):	Dade Behring Marburg GmbH, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6251581	B1	20010626	
APPLICATION INFO.:	US 1991-704569		19910522	(7)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Venkat, Jyothsna
ASSISTANT EXAMINER:	Ponnaluri, P.
LEGAL REPRESENTATIVE:	Finnegan, Henderson, Farabow, Garrett & Dunner L.L.P., Gattari, Patrick G
NUMBER OF CLAIMS:	36
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	8 Drawing Figure(s); 4 Drawing Page(s)

LINE COUNT: 3221
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . comprising a suspendible particle having incorporated therein a chemiluminescent compound where the particle has an sbp member bound thereto. The **composition** can further comprise a suspendible particle having a photosensitizer incorporated therein.

SUMM Another embodiment of the invention concerns kits comprising in packaged combination a **composition** that includes (1) a suspendible particle having a chemiluminescent compound where the particle has an sbp member bound thereto, and (2) a photosensitizer. The kit can further include a **composition** comprising a second suspendible particle comprising a photosensitizer where the particle has an sbp member bound thereto.

DETD In one aspect of the present invention a **composition** comprising a photosensitizer and a ligand, receptor or polynucleotide binds in an assay to a **composition** comprising a chemiluminescent compound and a ligand, receptor or polynucleotide. The chemiluminescent compound can react with singlet oxygen and the. . . the photosensitizer usually by irradiation of the photosensitizer. Singlet oxygen produced by the photosensitizer that is not bound to the **composition** comprising a chemiluminescent compound is unable to reach the chemiluminescent compound before undergoing decay (t.sub.1/2 is about two microseconds in water). The **composition** comprising a photosensitizer that becomes bound to the **composition** comprising the chemiluminescent compound produces singlet oxygen that reacts with the chemiluminescent compound because such singlet oxygen can survive the. . . has a much longer lifetime, namely, greater than about one hundred microseconds. The analyte must modulate the binding between the **composition** comprising the photosensitizer and the **composition** comprising the chemiluminescent compound. Usually, at least one of the chemiluminescent compound and the photosensitizer is associated with a surface,. . .

DETD Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

DETD . . . Spore-forming Bacilli Phialophora jeanselmei

Bacillus anthracis	Microsporum gypseum
Bacillus subtilis	Trichophyton mentagrophytes
Bacillus megaterium	Keratinomyces ajelloi
Bacillus cereus	Microsporum canis
Anaerobic Spore-forming Bacilli	Trichophyton rubrum
Clostridium **botulinum**	Microsporum adouini
Clostridium tetani	Viruses
Clostridium perfringens	Adenoviruses
Clostridium novyi	Herpes Viruses
Clostridium septicum	Herpes simplex
Clostridium histoyticum	Varicella (Chicken pox)
Clostridium tertium	Herpes Zoster (Shingles)

Clostridium. . .

DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD . . . both compounds to associate with the same particle. This possibly can be further reduced by utilizing particles of only one **composition** that are associated with either the photosensitizer or chemiluminescent compound or by using two types of particles that differ in **composition** so as to favor association of the photosensitizer with one type of particle and association of the chemiluminescent compound with. . .

DETD . . . combined in one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises (1) a **composition** comprising a suspendible particle comprising a chemiluminescent compound, the particle having an sbp member bound to it, and (2) a. . .

CLM What is claimed is:

1. A **composition** comprising: a) first suspendible particles comprising a chemiluminescent compound capable of reacting with singlet oxygen, and b) second suspendible particles. . .

2. The **composition** of claim 1, wherein said first suspendible particles have bound thereto a specific binding pair member.

3. The **composition** of claim 2, wherein said first suspendible particles are selected from the group consisting of latex particles, lipid bilayers, oil. . .

4. The **composition** of claim 2, wherein said chemiluminescent compound contains an olefin group.

5. The **composition** of claim 2, wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .

6. The **composition** of claim 2, wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-alkyl acridans, enolethers, enamines, and 9-alkylidene. . .

7. The **composition** of claim 2, wherein said specific binding pair member is selected from the group consisting of receptors, ligands, and polynucleotides.

. . .

8. The **composition** of claim 1, wherein said second suspendible particles are selected from the group consisting of latex, lipid bilayers, oil droplets,. . .

9. The **composition** of claim 1, wherein said second suspendible particles have bound thereto a specific binding pair member.

10. The **composition** of claim 9, wherein said specific binding pair member is selected from the group consisting of receptors, ligands, and polynucleotides.

. . .

11. A **composition** comprising: a) first suspendible particles comprising a chemiluminescent compound that is capable of reacting with singlet oxygen, wherein said first. . .

12. The **composition** of claim 11, wherein said chemiluminescent compound contains an olefin group.

13. The **composition** of claim 11, wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .

14. The **composition** of claim 11, wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-alkyl acridans, enolethers, enamines, and 9-alkylidene. . .

15. The **composition** of claim 11, wherein said first specific binding pair member is selected from the group consisting of receptors, ligands, and. . .
16. The **composition** of claim 11, wherein said second specific binding pair member is selected from the group consisting of receptors, ligands, and. . .
17. The **composition** of claim 11, wherein said first suspendible particles, said second suspendible particles, or both, are latex particles.

18. A kit comprising: (a) a first **composition** comprising a member of a specific binding pair (sbp) member associated, via at least one covalent or non-covalent bond, with. . . in its excited state of activating oxygen to its singlet state, and ii) a suspendible particle; and (b) a second **composition** comprising an sbp member associated, via at least one covalent or non-covalent bond, with i) a chemiluminescent compound, capable of. . .
19. The kit of claim 18, wherein the suspendible particle in said first **composition**, said second **composition**, or both, is a latex particle.

20. The kit of claim 18, wherein said second **composition** further comprises a fluorescent energy acceptor.

23. A kit comprising: (a) a first **composition** comprising an antibody as a member of a specific binding pair (sbp) associated, via at least one covalent or non-covalent. . . its excited state of activating oxygen to a singlet state, and ii) a suspendible latex particle; and (b) a second **composition** comprising an antibody as a sbp member associated, via at least one covalent or non-covalent bond, with i) an enol. . .
25. The kit of claim 23, wherein said second **composition** further comprises a fluorescent energy acceptor.

27. A kit comprising, in packaged combination, a) a **composition** comprising a first suspendible particle, wherein said first suspendible particle comprises a chemiluminescent compound capable of emitting light upon interaction. . . oxygen, and wherein said first suspendible particle is bound to a first specific binding pair (sbp) member, and b) a **composition** comprising a second suspendible particle, wherein said second suspendible particle comprises a photosensitizer capable, in its excited state, of activating. . .

L16 ANSWER 8 OF 50 USPATFULL

ACCESSION NUMBER:	2000:174129 USPATFULL
TITLE:	Preparation for the application of agents in mini-droplets
INVENTOR(S):	Cevc, Gregor, Heimstetten, Germany, Federal Republic of
PATENT ASSIGNEE(S):	Idea AG, Munich, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6165500		20001226	
APPLICATION INFO.:	US 1992-844664		19920408	(7)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1990-4026834	19900824
	DE 1990-4026833	19900824
	DE 1991-4107153	19910306
	WO 1991-EP1596	19910822

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted

PRIMARY EXAMINER: Kishore, Gollamudi S.
LEGAL REPRESENTATIVE: Davidson, Davidson & Kappel, LLC
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 31 Drawing Figure(s); 21 Drawing Page(s)
LINE COUNT: 4336
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . acids) and of lipid vesicles, Gesztes und Mezei (1988, Anesth. Analg. 67, 1079-1081) have succeeded in inducing local analgesia with **lidocaine**-containing carriers; however, the overall effectiveness of the drug in this preparation was relatively low and its effects were only observed. . .

DETD . . . optimized for applications on skin (cf. patent application P 40 26 834.9-41) was based on the use of a carrier **composition** with an optimal lipid/surfactant ratio in the range of L/S=1-40/1. However, a transfersome must mainly have an optimal elasticity, which. . .

DETD . . . medical agents. Transfersomes can carry water- or fat-soluble agents to various depths at the application site, depending on the transfersomal **composition**, application dose, and form. Special properties which cause a carrier to behave as a transfersome can be realized for phospholipid. . .

DETD at least one agent which can induce systemic anesthesia or analgesia, e.g. chlorobutanol, ketamine, **oxetacaine**, propanidide and thiamylal, aminophenol-derivatives, aminophenazol-derivatives, antranilic acid- and arylpropione acid derivatives, azapropazone, bumadizone, chloroquin- and codeine-derivatives, diclophenac, fentanil, ibuprofen, indometacine,. . . acid, meptazonol, methadone, mofebutazone, nalbufine, Na-salt of noramidopyrinium-methanesulfonate, nefopam, normethadone, oxycodone, paracetamol, pentazocine, pethidine, phenacetine, phenazocine, phenoperidine, pholcodine, piperylone, piritramide, **procaine**, propyphenazone, salicylamide, thebacone, tiemonium-odide, tramadone;

DETD . . . such as most of the cardiacs and beta-blockers, ajmaline, bupranolol, chinidine, digoxine derivatives, diltiazem, disopyramidedihydrogensulfate, erythromycine, disopyramide, gallopamil, ipratropiumbromide, lanatoside, **lidocaine**, lorcainide, orciprenalinesulfate, **procaine** amide, propafenone, sparteinesulfate, verapamil, toliprolol.

DETD at least one substance with a neurotherapeutic activity, such as anaesthetics and vitamins, atropine-derivatives, benfotiamine, choline-derivatives, caffeine, cyanocobolamine, alpha-liponic acid, **mepivacaine**, phenobarbital, scopolamine, thiaminchloride hydrochloride, etc., and, most notably, **procaine**;

DETD at least one sympathicomimetic, e.g. bamethane, buphenine, cyclopentamine, dopamine, L-(-)-ephedrine, **epinephrine**, etilefrine, heptaminol, isoetarine, metaraminol, methamphetamine, methoxamine, norfenefrine, phenylpropanolamine, pholedrine, propylhexedrine, protokylol or synephrine;

DETD at least one substance with a vasoconstricting action; often, adrenalone, **epinephrine**, felypressine, methoxamine, naphazoline, oxymetazoline, tetryzoline, tramazoline or xylometazoline are used for this purpose;

DETD . . . aflatoxin B2-alpha, aflatoxin G1, aflatoxin G2, aflatoxin G2-alpha, aflatoxin M1, aflatoxin M2, aflatoxin P1, aflatoxin Q1, alternariol-monomethyl ether, aurovertin B, **botulinum** toxin D, cholera toxin, citreoviridin, citrinin, cyclopiazonic acid, cytochalasin A, cytochalasin B, cytochalasin C, cyrochalasin D, cytochalasin, cytochalasin H, cytochalasin. . .

DETD . . . example, acetylcholine, adrenaline, adrenocorticotropic hormone, angiotensine, antidiuretic hormone, cholecystokinine, chorionic gonadotropine, corticotropine A, danazol, diethylstilbestrol, diethylstilbestrol glucuronide, 13,14-dihydro-15-keto-prostaglandins, 1-(3',4'-dihydroxyphenyl)-2-aminoethanol, 5,6-dihydroxytryptamine,

epinephrine, follicle stimulating hormone, gastrin, gonadotropin, .beta.-hypophamine, insulin, juvenile hormone, 6-ketoprostaglandins, 15-ketoprostaglandins, LTH, luteinizing hormone releasing hormone, luteotropic hormone, .alpha.-melanocyte stimulating. . .

DETD . . . to be a complex function of the carrier size, often showing a maximum depending on the chosen carrier and/or agent **composition** .

DETD . . . active substances with a tendency to leave carriers and move into a barrier give rise to a locally variable carrier **composition**, etc. These interdependencies should be thought of and considered prior to each individual application. In the search for a set. . .

DETD Next, the carrier **composition** or concentration is adapted by reducing the edge activity in the system to an extent which ensures the vesicle stability. . . the one hand, a mechanical tendency of the carrier components to "stay together"; on the other hand, that the carrier **composition** during the transport, and in particular during the permeation process, does not change at all or not much. The position. . .

DETD . . . body systems through a system of blood and lymph vessels, the precise drug fate being dependent on the carrier size, **composition** and formulation.

DETD . . . cm of skin surface, the given masses pertaining to the basic carrier substance. The optimal mass depends on the carrier **composition**, desired penetration depth and duration of action, as well as on the detailed application site. Application doses useful in agrotechnics. . .

DETD **Composition**:

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DETD . . . suspensions independent of the precise L/S ratio; 10 weight-% of agent cannot be incorporated into stable transfersomes of the given **composition**.

DETD **Composition**:

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DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

L16 ANSWER 9 OF 50 USPATFULL
ACCESSION NUMBER: 2000:121520 USPATFULL
TITLE: Method for treating painful conditions of the anal region and compositions therefor
INVENTOR(S): Fogel, Barry S., Waban, MA, United States
PATENT ASSIGNEE(S): Synchroneuron, LLC, Waban, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6117877		20000912
APPLICATION INFO.:	US 1999-258828		19990225 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-31858, filed on 27 Feb 1998
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Cook, Rebecca
LEGAL REPRESENTATIVE: Choate, Hall & Stewart
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
LINE COUNT: 1104
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Method and **composition** for treating painful conditions of the anorectal region. The compositions include a combination of an .alpha.-adrenergic blocker and sucralfate, a combination of .alpha.-adrenergic blocker and **lidocaine**, and a combination of an .alpha.-adrenergic blocker, **lidocaine**, and sucralfate. Alternatively, the **composition** may contain only an .alpha.-adrenergic blocker. Additional active ingredients for reduction of anal pain may be added to the **composition**, particularly capsaicin. The compositions may be included in a petrolatum base along with a water soluble lubricant. These compositions have. . .

SUMM . . . determined by the intensity of the contraction of the IAS. These treatments include lateral sphincterotomy, injection of the sphincter with **botulinum** toxin (Maria et al., Ann Surg, 1998 November, 228(5):664-9), and application of nitroglycerin ointment (Manookian et al.; Ann Surg 1998. . . of treatment for chronic anal fissures recommends beginning with nitroglycerin ointment. If the fissure has not healed in six weeks, **botulinum** toxin injections are given. That review notes that "considerable educational effort is required to successfully adjust the dose" of nitroglycerin. .

SUMM . . . minutes. A separate approach, described by Parischa and Kallo in U.S. Pat. No. 5,437,291, makes use of direct injections of **botulinum** toxin into the affected area for treatment of gastrointestinal muscle disorders and other smooth muscle dysfunction. They report that the benefits of **botulinum** toxin injection appear to be sustained for several months.

SUMM **Lidocaine**, a topical anesthetic, has been used as a treatment for another painful rectal condition, ulcerative proctitis (Bjorck et al., Scandinavian. . .

SUMM In co-pending, commonly-owned U.S. patent application Ser. No. 09/031,858, incorporated by reference herein, I show that sucralfate, together with nitroglycerin, **lidocaine**, or both, is efficacious for the treatment of anal fissures, and inferred its utility for other painful conditions of the. . .

SUMM One aspect of the invention is a **composition** comprising an .alpha.-adrenergic blocker alone at an effective and tolerable dose. Another aspect of the present invention is a **composition** comprising the combination of an .alpha.-adrenergic blocker together with sucralfate. Yet another aspect is a **composition** comprising a combination of an .alpha.-adrenergic blocker together with

a local anesthetic (preferably **lidocaine**). In addition, the inventive **composition** may combine .alpha.-adrenergic blocker, together with sucralfate and a local anesthetic to achieve a synergistic effect. These compositions have analgesic. . .

SUMM . . . analgesic effect. One particularly preferred active ingredient is capsaicin. According to the present invention, capsaicin may be added to any **composition** for treatment of anal pain. Continued capsaicin treatment, may be effective in reducing some of the reflex contractions of the. . .

SUMM . . . symptoms, with tolerable adverse effects. A person skilled in the art will recognize that the optimal dose of a pharmaceutical **composition** administered will vary from one individual to another. When considering a topical preparation for anorectal use, dosage in individual patients--regarding. . .

SUMM "Non-toxic": As used herein, "non-toxic" refers to the administration of a dose of the **composition** for treatment of anal pain, wherein the active components in the **composition** cause no adverse effects intolerable to the patient onto which the **composition** is administered.

SUMM "Active agent": "Active agent", as used herein, refers to any component in a **composition** of the present invention that increases the analgesic effects of that **composition** and can be added to the compositions of the present invention to enhance their ability to reduce the symptoms associated with anorectal disease. In the **composition** of the present invention, .alpha.-blockers, **lidocaine** and sucralfate are all active agents. "Active agent" is also used to refer to any component in any known **composition** (e.g. preparation H) that increase the analgesic effects of that **composition**.

SUMM . . . differs from the use of "active agent", as used herein, to mean any component that can be added to a **composition** that has some biological effect, whether the biological effect is directly related to anorectal disease or not. The biological effect. . .

SUMM . . . is used generally to refer to anything with relevant biological activity that is added to biologically inert ingredients in a **composition** intended for therapeutic use.

DETD . . . and antagonists, the IAS responds like the internal urethral sphincter, with which it shares a common developmental origin. As expected, **phenylephrine**, an .alpha.1 agonist, increases tone in the IAS. However, it is unexpected that a tolerable dose of an .alpha.-adrenergic blocker. . .

DETD . . . Case Report 3). Within 5 minutes, she had substantial relief-->50%. She compared the cream with a combination cream containing nitroglycerin, **lidocaine** and sucralfate; results were similar. The patient had a headache after applying the cream with nitroglycerin, but did not experience. . .

DETD As noted above, in co-pending patent application Ser. No. 09/031,858, I reported that a cream containing nitroglycerin, **lidocaine**, and sucralfate was efficacious for the treatment of the pain of anal fissures, and that it was more efficacious than nitroglycerin alone, or nitroglycerin with **lidocaine**, **lidocaine** and sucralfate alone, or nitroglycerin and sucralfate alone.

DETD Three factors contribute to the synergistic efficacy of the combination: 1) the local anesthetic effect of **lidocaine** is based on a different mechanism of action than the analgesic effect of nitroglycerin; 2) sucralfate serves to keep the. . . the efficacy of an .alpha.1-adrenergic blocker alone for anal pain, I inferred that the combination of an .alpha.1-adrenergic blocker with **lidocaine** and sucralfate, or with **lidocaine** or sucralfate alone, would provide relief from anal pain. Such combination would circumvent the use of nitroglycerin, which, as noted. . . above, causes adverse side effects, especially headaches, in some patients. In addition, the combined use of an .alpha.-adrenergic blocker with **lidocaine** and sucralfate provides therapeutic efficacy at a lower than toxic dose

of the .alpha.-adrenergic blocker due to the synergistic activity. . .

DETD . . . for treatment of painful anal conditions. One skilled in the art will recognize any local anesthetic, such as, without limitation, **lidocaine**, **benzocaine**, **dibucaine** **bupivacaine**, **tetracaine** etc., is acceptable for use in the present invention. Preferred local anesthetics include **lidocaine**, **benzocaine**, **dibucaine**, and **bupivacaine**. A most preferred local anesthetic is **lidocaine**.

DETD It is preferable that any **composition** described herein is administered at effective and non-toxic dosages, such that the patient experiences relief from symptoms in the absence. . . in the dose range of 0.1-1.0 mg per 5 ml of formula. A local anesthetic of the same potency as **lidocaine** would be administered at a concentration in the dose range of 20-200 mg per 5 ml of formula. Sucralfate is typically administered at 50-500 mg per 5 ml of formula. A particularly preferred **composition** of the present invention is a **composition** in which each standard 5 ml dose contains 0.1-1.0 mg of doxazosin or terazosin, 20-200 mg of **lidocaine**, and 50-500 mg of sucralfate. Specific concentrations may be adjusted according to patient tolerance. Dosage in individual patients--regarding the concentration. . .

DETD . . . present invention provides compositions containing .alpha.-adrenergic blockers and additional active ingredients. One particularly attractive active ingredient of the present inventive **composition** is capsaicin.

DETD . . . U.S. Pat. No. 5,788,982 by Nadoolman, et al., and U.S. Pat. No. 4,997,853 by Bernstein describes co-administration of capsaicin and **lidocaine** generally to the skin, to reduce the burning associated with the application of capsaicin alone. U.S. Pat. No. 5,854,291 by. . . an individual with a painful anal condition. Thus, I proposed that the active ingredient capsaicin may be added to any **composition** for treatment of anal pain.

DETD . . . antiinflammatory drug (including specifically diclofenac opiates), a local anesthetic, sucralfate or a similar disaccharide, capsaicin (with a local anesthetic, i.e., **lidocaine**) or capsaicin (in a tolerable dosage or preparation). Such combinations would provide improved relief over treatment with the .alpha.-antagonist alone.

DETD . . . treatment of anorectal conditions, including without limitation Anusol, Tronolane, Preparation H, and generic equivalents of those products. Other examples are A-**Caine**, Americane, Anusol, Balneol, BiCozene, Blue-Gray, Calmol 4, Cortef Rectal Itch Ointment, Diothane, **Epinephiricaine** Ointment, Gentzy Wipes, Hemorrin, HTO Ointment, HTO Stainless, Lancane, Mediconet, Non-Steroid Protofoam, Nupercainal Ointment, Nupercainal Suppositories, Pazo, Perifoam, Peterson's Ointment, **Pontocaine**, Preparation H Cleansing Pads, Proctodon, Rantex, Rectal Medicone Suppositories, Rectal Medicone Unquent, **Tanicaine** Ointment, **Tanicaine** Suppositories, Tucks Cream and Ointment, Tucks Pads, Wyanoid Ointment and Wyanoid Suppositories. See also Federal Register, 45 33576, May 22,. . .

DETD . . . or reducing IAS pressure, including without limitation nitroglycerin, other nitrates (e.g. isosorbide dinitrate), other nitric oxide donors, and L-arginine. Any **composition** containing any one of these ingredients could be reformulated to contain an .alpha.-adrenergic blocker, (i.e., an .alpha.1-adrenergic antagonist or a non-specific .alpha.-adrenergic antagonists with sufficient .alpha.1-adrenergic antagonist effects.). Alternatively, capsaicin, with or without a local anesthetic such as **lidocaine**, can be used to replace the active agents or ingredients in the above-mentioned marketed over-the-counter compositions.

DETD . . . temporarily relieve pain, burning, itching, discomfort and irritation by preventing transmission of nerve impulses. Non-limiting

examples of topical anesthetics include **benzocaine**, pramoxine hydrochloride, benzyl alcohol, **dibucaine** hydrochloride, dicylonine hydrochloride, **lidocaine**, **tetracaine** and **tetracaine** hydrochloride. See also Federal Register, 45 35576, May 27, 1980. In general, the local or topical anesthetic may be present. . .

DETD . . . reduce inflammation, irritation and swelling by constricting the symptomatic abnormally large conglomerates of blood vessels. Non-limiting examples include ephedrine and **epinephrine**. See also Federal Register, 45 35576, May 27, 1980.

DETD . . . capsaicin and other pharmacologic compounds used in the treatment of the symptoms of anorectal disease are formulated in the same **composition**, for example with a wound healing compound, a protectant, a vasoconstrictor, or a local anesthetic or with more than one. . .

DETD Compositions in the form of ointments, creams, gels, pastes, suppositories, pads, liquids, emulsions, foams, aerosols, semisolid powders, or any other **composition** suitable for topical administration are acceptable compositions for the topical treatment of the anorectal pain. In another aspect, the **composition** of the invention may contain conventional materials and ingredients and conform to pharmacologically accepted formulations. Some of the compositions listed. . . inflamed tissues and sphincter muscle fibers, and providing more accurate and controllable dosing. Accidental spilling and undesired contact with the **composition** can also be minimized with such types of formulations.

DETD . . . glycols and similar agents, as they are readily compatible with water or other diluents which may be formulated in the **composition**. Alternatively, an emulsion base may be employed to impart the desired thickening effect, as well as the emollient effect of. . .

DETD . . . like of different viscosities depending upon the desired consistency and concentration of active compound(s) which may be incorporated into the **composition**. Other thickening agents which may be suitable for employment herein include but are not limited to water-dispersible gums, carboxyvinyl polymers,. . .

DETD . . . dosage forms. Squeeze tubes for lotions and ointments and cofton stick applicators may be employed for topical application of the **composition** for liquids ranging from those of water-like viscosity of the more viscous formulations of thickened compositions and for powders and. . .

DETD In treatments according to the invention, an amount of the **composition** of the invention is contacted with or applied to the affected anal area or proximate thereto such that an effective amount of .alpha.-adrenergic antagonist or other active compound is administered. The amount of active compound(s) or **composition** which is employed should be effective for the amelioration, control and/or healing of the anal disease and for the prompt and dramatic control or relief of pain resulting from or associated with the disease. For example, an ointment **composition** of the invention can be applied topically at each application to the external anus and to the distal anal canal. . .

DETD . . . Series 2: 4 subsequent patients, all but one with anoscopically confirmed anal fissures, were treated with the combination of nitroglycerin, **lidocaine**, and sucralfate, with the expectation of even better relief. (Patient #4 suffered from chronic anal pain of unknown cause.) All. . .

DETD . . . required any oral analgesics, sitz baths, or other treatments to relieve pain, as soon as they had access to the nitroglycerin-**lidocaine**-sucralfate cream.

DETD . . . treated. He had six weeks of pain prior to the treatment. We treated him on alternate days with either the **composition** including nitroglycerin, **lidocaine** and sucralfate or the **composition** without the sucralfate. He was instructed to reapply

the formula any time the pain began to recur. The three ingredient. . .

DETD . . . anal fissure can be lower than that reported in the literature. These cases also show that adding nitroglycerin to the sucralfate-**lidocaine** combination improves efficacy. The three additional cases are shown in the table below:

DETD Patient #5 in the table above received the nitroglycerin-**lidocaine**-sucralfate formula discussed above (formula A) and a formulation without sucralfate (formula B) in the sequence A-B-A over three days. The. . .

DETD Patient #6 received a modified formula with 30 grams of 2% nitroglycerin ointment per 500 grams of the nitroglycerin-**lidocaine** -sucralfate mixture. The concentration of nitroglycerin in this mixture (0.12%) was lower than the 0.2% concentration reported in recent randomized controlled. . . cause headaches (or any other side effects). This case supports the inventor's premise that nitroglycerin in combination with sucralfate and **lidocaine** is superior to nitroglycerin alone. The combination is efficacious at lower doses of nitroglycerin and the combination is less likely. . .

DETD . . . that contains nitroglycerin will be more efficacious if it also contains sucralfate. A cream or ointment containing nitroglycerin, sucralfate, and **lidocaine** is especially efficacious.

DETD . . . Within 5 minutes, the patient has substantial relief (>50%). The patient compared the .alpha.-adrenergic cream with a cream containing nitroglycerin, **lidocaine** and sucralfate and reported that relief was similar. The patient chose to continue using the doxazosin cream.

DETD 10 grams **lidocaine** base

DETD Conclusions: Case Reports 4 and 5 establish that a combination of **lidocaine**, sucralfate and an .alpha.1-adrenergic antagonist is efficacious and tolerable treatment for anal fissures. Together with Case Report 3, showing that. . . .alpha.1-adrenergic antagonist alone is efficacious, it can be inferred that the combination of an .alpha.1-adrenergic antagonist with either sucralfate or **lidocaine** (rather than both) will be efficacious.

DETD . . . potential usefulness of capsaicin in the anal region, I did an experiment on the tolerability of capsaicin alone and with **lidocaine**, and with **lidocaine** and dozasosin. A small amount of 0.075% capsaicin cream amount (about 5 mm of Zostrix.RTM. cream, as it comes from. . . with copious amounts of water. The same amount of capsaicin cream was then combined with an equal amount of 5% **lidocaine-prilocaine** cream (EMLA.RTM. Cream), The burning sensation was present, but was tolerable. Finally, the same amount of capsaicin cream was combined with the above described doxazosin-**lidocaine**-sucralfate cream. The burning sensation was less than with the EMLA Cream, and was easily tolerated.

DETD . . . of a local anesthetic, capsaicin, with its known local analgesic properties, becomes a safe and effective active ingredient in a **composition** for the relief of anal pain. It would be expected to augment the effects of ingredients that work by different. . .

DETD . . . single agents, or combinations of two agents. In particular, the combination of nitroglycerin or an .alpha.1-adrenergic blocker with sucralfate and **lidocaine** is particularly effective. Preparations of superior effectiveness combine an agent that relieves spasm of the IAS with a local anesthetic. . . administration, becomes tolerable when given in combination with a local anesthetic. It thus can be a useful addition to a **composition** for the treatment of anorectal pain, as long as that **composition** contains a local anesthetic ingredient.

DETD A triple combination of nitroglycerin, sucralfate, and **lidocaine** (or more generally a nitrate, sucralfate, and a local anesthetic) will produce more rapid, complete, and long-lasting relief than a **composition** with only one or two of the three ingredients. A

triple combination of an alpha 1-adrenergic blocker, sucralfate, and a local anesthetic will produce more rapid, complete and long-lasting relief than a **composition** with only one or two of the three ingredients. Despite the availability of all of these ingredients for many years, . . . nitroglycerin will have lesser side effects than an equally effective dose of nitroglycerin alone. Experience with the combination of nitroglycerin, **lidocaine**, and sucralfate suggests that it does have less side effects than nitroglycerin, either because less nitroglycerin is used by the. . .

CLM What is claimed is:

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker; and applying an effective dose of the **composition** to the anal region.

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker and sucralfate; and applying an effective dose of the **composition** to the anal region.

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker and a local anesthetic; and applying an effective dose of the **composition** to the anal region.

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker, a local anesthetic and sucralfate; and applying an effective dose of the **composition** to the anal region.

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker, a local anesthetic and capsaicin; and applying an effective dose of the **composition** to the anal region.

. . . 10. The method of claim 3, 4 or 5, wherein the local anesthetic is selected from the group consisting of: **lidocaine**, **benzocaine**, **bupivacaine**, and **tetracaine**.

. . . after the step of providing and before the step of applying, the method further comprises the step of: mixing the **composition** with a cream, gel, paste, lotion, ointment, aerosol, suppository, pad, liquid, emulsion, foam or, semisolid powder or a combination thereof.

. . .

12. The method of claim 1, 2, 3, 4, or 5 wherein the **composition** further comprises a cream, gel, paste, lotion, ointment, aerosol, suppository, pad, liquid, emulsion, foam or semisolid powder or a combination. . .

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker, a local anesthetic and sucralfate in a base of petrolatum, and further comprising a water soluble lubricant; and applying an effective dose of the **composition** to the anal region.

17. The method of claim 16 wherein the **composition** comprises approximately 0.1-1.0 milligrams of doxazosin or terazosin per 5 milliliters of **composition**, approximately 20-200 milligrams of **lidocaine** base per 5 milliliters of **composition**, and approximately 50-500 milligrams of sucralfate per 5 milliliters of

composition.

18. The method of claim 16 wherein the local anesthetic is **lidocaine**.

L16 ANSWER 10 OF 50 USPATFULL
ACCESSION NUMBER: 1999:163855 USPATFULL
TITLE: Chemiluminescent compounds and methods of use
INVENTOR(S): Singh, Sharat, San Jose, CA, United States
Singh, Rajendra, Mountain View, CA, United States
Meneghini, Frank, Keene, NH, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Dade Behring Marburg GmbH, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6002000		19991214
APPLICATION INFO.:	US 1996-661849		19960611 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-373678, filed on 17 Jan 1995, now patented, Pat. No. US 5545834 which is a continuation of Ser. No. US 1992-916453, filed on 20 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ford, John M.
ASSISTANT EXAMINER: Kifle, Bruck
LEGAL REPRESENTATIVE: Leitereg, Theodore J
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1805
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .
DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
DETD . . . Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tubercolosis hominis
Mycobacterium. . .
DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan,

their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polynucleotide: a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD . . . context of the present invention, a ligand conjugated to a chemiluminescent label of this invention, is a ligand-label conjugate. A **composition** which is described as comprising subunit A conjugated to subunit B is a **composition** wherein subunit A is bound to subunit B.

DETD One embodiment of the present invention pertains to a chemiluminescent **composition** comprising a chemiluminescent compound of this invention in a pH 6-10 aqueous solution containing hydrogen peroxide or a means for. . . a hapten or an antibody, in the manner described above. Compound (I) is particularly suited for use in such a **composition**. If peroxide is to be detected, it will usually be desirable to have a relatively high concentration of the chemiluminescent. . .

DETD Another embodiment of the present invention is a light emitting chemical **composition** comprised of hydrogen peroxide and a chemiluminescent compound of this invention, for example, Compound (II). It is usually desirable to. . .

DETD . . . compound can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD One such kit comprises in packaged combination (1) a **composition** comprising a chemiluminescent compound of this invention, for example Compound (I), having bound thereto a specific binding pair member and. . . of hydrogen peroxide or an analyte that modulates the formation of hydrogen peroxide, and comprises in packaged combination (1) a **composition** comprising the compound A--L--Q described herein and (2) any ancillary reagents required to produce hydrogen peroxide from said analyte when. . .

CLM What is claimed is:

5. A chemiluminescent **composition** comprised of the compound of claim 1 in a pH 6-10 aqueous solution containing hydrogen peroxide.

6. A light emitting chemical **composition** comprising hydrogen peroxide and a compound having the following formula: wherein: X' is O or S and Y' is N. . .

7. The **composition** of claim 6 which further comprises a catalyst.

L16 ANSWER 11 OF 50 USPATFULL
ACCESSION NUMBER: 1999:92783 USPATFULL
TITLE: Chemiluminescent compounds and methods of use
INVENTOR(S): Singh, Sharat, San Jose, CA, United States

Singh, Rajendra, Mountain View, CA, United States
Meneghini, Frank, Keene, NH, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Dade Behring Marburg GmbH, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5936070		19990810
APPLICATION INFO.:	US 1996-664269		19960611 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-373678, filed on 17 Jan 1995, now patented, Pat. No. US 5545834 which is a continuation of Ser. No. US 1992-916453, filed on 20 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ceperley, Mary E.
LEGAL REPRESENTATIVE: Leitereg, Theodore J
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1818
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .
DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
DETD . . . group
Hemophilus influenzae
H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae

Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polynucleotide: a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD . . . context of the present invention, a ligand conjugated to a chemiluminescent label of this invention, is a ligand-label conjugate. A **composition** which is described as comprising subunit A conjugated to subunit B is a **composition** wherein subunit A is bound to subunit B.

DETD One embodiment of the present invention pertains to a chemiluminescent **composition** comprising a chemiluminescent compound of this invention in a pH 6-10 aqueous solution containing hydrogen peroxide or a means for. . . a hapten or an antibody, in the manner described above. Compound (I) is particularly suited for use in such a **composition**. If peroxide is to be detected, it will usually be desirable to have a relatively high concentration of the chemiluminescent. . .

DETD Another embodiment of the present invention is a light emitting chemical **composition** comprised of hydrogen peroxide and a chemiluminescent compound of this invention, for example, Compound (II). It is usually desirable to. . .

DETD . . . compound can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD One such kit comprises in packaged combination (1) a **composition** comprising a chemiluminescent compound of this invention, for example Compound (I), having bound thereto a specific binding pair member and. . . of hydrogen peroxide or an analyte that modulates the formation of hydrogen peroxide, and comprises in packaged combination (1) a **composition** comprising the compound A--L--Q described herein and (2) any ancillary reagents required to produce hydrogen peroxide from said analyte when. . .

CLM What is claimed is:

5. A chemiluminescent **composition** comprised of the compound of claim 1 in a pH 6-10 aqueous solution containing hydrogen peroxide.

6. A light emitting chemical **composition** comprising hydrogen peroxide and a compound having the following formula: ##STR33## wherein:

X' and Y' are linking groups each comprising. . .
7. The **composition** of claim 6, which further comprises a catalyst.

L16 ANSWER 12 OF 50 USPATFULL

ACCESSION NUMBER:	1998:72421 USPATFULL
TITLE:	Method of separation employing magnetic particles and second medium
INVENTOR(S):	Vorpahl, John, Livermore, CA, United States
PATENT ASSIGNEE(S):	Dade Behring Marburg GmbH, Deerfield, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5770388		19980623
APPLICATION INFO.:	US 1993-168263		19931213 (8)
DISCLAIMER DATE:	20110118		
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1989-455550, filed on 22 Dec 1989, now patented, Pat. No. US 5279936		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Wolski, Susan		
LEGAL REPRESENTATIVE:	Jordan, Leland K, Rosenstock, Jerome, Leitereg, Theodore J.		
NUMBER OF CLAIMS:	19		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1449		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Component of interest (CI)--the compound or **composition** to be separated. The component of interest can be non-particulate or particulate. Non-particulate CI can be comprised of a member. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzoyl ecgonine, their derivatives and metabolites, ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, and their metabolites.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . Spore-forming Bacilli

	Phialophora jeanselmei
Bacillus anthracis	Microsporum gypseum
Bacillus subtilis	Trichophyton mentagrophytes
Bacillus megaterium	Keratinomyces ajelloi
Bacillus cereus	Microsporum canis
Anaerobic Spore-forming Bacilli	
	Trichophyton rubrum
Clostridium **botulinum**	Microsporum adouini
Clostridium tetani	Viruses
Clostridium perfringens	
	Adenoviruses
Clostridium novyi	Herpes Viruses
Clostridium septicum	Herpes simplex
Clostridium histolyticum	
	Varicella (Chicken pox)

Clostridium tertium Herpes Zoster (Shingles)
Clostridium. . .
SUMM Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .
SUMM Polyionic reagent--a compound, **composition**, or material, either inorganic or organic, naturally occurring or synthetic, having at least two of the same charge, either polyanionic. . .
SUMM Releasing agent--a compound, **composition**, or material, either naturally occurring or synthetic, organic or inorganic, capable of reversing the non-specific binding between, i.e., dissociating, particulate. . .
SUMM The invention further comprises a **composition** comprising (1) a first liquid medium containing magnetic particles to which are bound a component of interest (CI) and in. . . therewith (2) a second liquid medium having a different density and/or viscosity or immiscibility with the first liquid medium. The **composition** may further comprise a polyionic reagent of opposite charge to the magnetic particles. Alternatively, in the **composition** of the invention the magnetic particles can have a CI bound to an sbp member bound thereto.

L16 ANSWER 13 OF 50 USPATFULL
ACCESSION NUMBER: 1998:57716 USPATFULL
TITLE: Aptamers specific for biomolecules and methods of making
INVENTOR(S): Griffin, Linda, Atherton, CA, United States
Albrecht, Glenn, Redwood City, CA, United States
Latham, John, Palo Alto, CA, United States
Leung, Lawrence, Hillsborough, CA, United States
Vermaas, Eric, Oakland, CA, United States
Toole, John J., Burlingame, CA, United States
PATENT ASSIGNEE(S): Gilead Sciences, Inc., Foster City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5756291		19980526
APPLICATION INFO.:	US 1995-484192		19950607 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-934387, filed on 21 Aug 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Zitomer, Stephanie W.
LEGAL REPRESENTATIVE: Bosse, Mark L.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 8242
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . "consensus sequence" means that certain positions, not necessarily contiguous, of an oligonucleotide are specified. By specified is meant that the **composition** of the position is other than completely random. Not all oligonucleotides in a mixture may have the same nucleotide at. . .
DETD Another aspect of the invention (**Composition** A) is directed to a pharmaceutical **composition** for medical use comprising the aptamer of Aptamer A-I in admixture with a physiologically acceptable excipient.
DETD Another aspect of the invention (**Composition** B) is directed to a **composition** for diagnostic use which comprises the aptamer of Aptamer A-I.
DETD . . . X) is directed to the aptamer of Aptamer W wherein the extracellular protein is selected from the group consisting of

botulinum toxin and diphtheria toxin, collagenase, tumor necrosis factor, antithrombin III, interleukins, elastase, and PDGF (and) fibroblast growth factors.

DETD Another aspect of the invention (**Composition** C) is directed to a complex formed by a target molecule and the aptamer of Aptamer N-AX, AY, AZ, BA,. . .

DETD Another aspect of the invention (**Composition** D) is directed to a pharmaceutical **composition** for medical use comprising the aptamer of Aptamer N-AX, AY, AZ, BA, or BB in admixture with a physiologically acceptable. . .

DETD Another aspect of the invention (**Composition** E) is directed to a **composition** for diagnostic use which comprises the aptamer of Aptamer N-AX, AY, AZ, BA, or BB.

DETD Another aspect of the invention (**Composition** F) is directed to a conjugate for modulating immune response to a pathologic cell, comprising:

DETD Another aspect of the invention (**Composition** G) is directed to a conjugate according to **Composition** F wherein said targeting agent is selected from the group consisting of oligonucleotides, antibodies and ligands for cell surface receptors.

DETD Another aspect of the invention (**Composition** H) is directed to a conjugate according to **Composition** G wherein said targeting agent is the aptamer of Aptamer N-AX, AY, AZ, BA, or BB.

DETD Another aspect of the invention (**Composition** I) is directed to a conjugate according to **Composition** F wherein the immunomodulatory moiety is selected from the group consisting of peptides and carbohydrates.

DETD administering an amount effective to modulate immune response of a conjugate in accordance with **Composition** F.

DETD Another aspect of the invention (**Composition** J) is directed to a complex which comprises a target substance or a fragment of a target substance and at. . .

DETD Another aspect of the invention (**Composition** K) is directed to the complex of **Composition** J wherein said at least one specifically-bound oligonucleotide is flanked by primer sequences adapted to permit application of PCR to. . .

DETD Another aspect of the invention (**Composition** L) is directed to the complex of **Composition** J with the proviso that the target is other than an oligonucleotide.

DETD Another aspect of the invention (**Composition** M) is directed to a mixture of candidate aptamers comprising randomized nucleotide sequences, wherein said randomized sequences contain at least. . .

DETD Another aspect of the invention (**Composition** N) is directed to the mixture of **Composition** M wherein said randomized sequences are flanked by primer sequences adapted to permit application of PCR to said mixture.

DETD Another aspect of the invention (**Composition** O) is directed to the mixture of **Composition** M wherein said randomized sequences are single-stranded DNA.

DETD . . . any one of Aptamer BE-BH wherein the target molecule is a small molecule selected from the group consisting of -bungarotoxin, **botulinum** toxin and diphtheria toxin.

DETD Another aspect of the invention (**Composition** P) is directed to a complex formed by a target molecule and the aptamer of Aptamer BE-BH, CR, CS, CT,. . .

DETD Another aspect of the invention (**Composition** Q) is directed to a pharmaceutical **composition** for medical use comprising the aptamer of Aptamer BE-BH, CR, CS, CT, or CU in admixture with a physiologically acceptable. . .

DETD Another aspect of the invention (**Composition** R) is directed to a **composition** for diagnostic use which comprises the aptamer of Aptamer BE-BH, CR, CS, CT, or CU.

DETD Another aspect of the invention (**Composition** S) is directed to the aptamer of Aptamer BE-BH, CR, CS, CT, or CU coupled to an auxiliary

substance.

DETD Another aspect of the invention (**Composition** T) is directed to the aptamer of **Composition** S wherein said auxiliary substance is selected from the group consisting of a drug, a toxin, a solid support, and. . .

DETD Another aspect of the invention (**Composition** U) is directed to a complex which comprises a target substance and at least one specifically-bound oligonucleotide, which complex is. . .

DETD Another aspect of the invention (**Composition** V) is directed to a mixture of candidate aptamers comprising randomized nucleotide sequences, wherein said randomized sequences contain at least. . .

DETD Another aspect of the invention (**Composition** W) is directed to the mixture of **Composition** V wherein said randomized sequences are flanked by primer sequences adapted to permit application of PCR to said mixture.

DETD Another aspect of the invention (**Composition** X) is directed to a mixture of oligonucleotide segments useful as a starting material in the recovery of an aptamer. . .

DETD Another aspect of the invention (**Composition** Y) is directed to a complex which comprises a kinin target substance and its specifically bound oligonucleotide, which complex is. . .

DETD Another aspect of the invention (**Composition** Z) is directed to the complex of **Composition** Y wherein said target substance is bradykinin.

DETD Another aspect of the invention (**Composition** AA) is directed to a mixture of oligonucleotide segments useful as a starting material in the recovery of an aptamer. . .

DETD Another aspect of the invention (**Composition** AB) is directed to a complex which comprises a hydrophobic target substance and its specifically bound oligonucleotide, which complex is. . .

DETD Another aspect of the invention (**Composition** AC) is directed to the complex of **Composition** AB wherein said hydrophobic target substance is an eicosanoid.

DETD Another aspect of the invention (**Composition** AD) is directed to the complex of **Composition** AC wherein said eicosanoid is selected from the group consisting of prostaglandins, thromboxanes, leukotrienes and prostacyclin.

DETD Another aspect of the invention (**Composition** AE) is directed to the complex of **Composition** AD wherein said eicosanoid is PGF2.

DETD Another aspect of the invention (**Composition** AF) is directed to a conjugate for modulating immune response to a pathologic cell, comprising:

DETD Another aspect of the invention (**Composition** AG) is directed to a conjugate according to **Composition** AF, wherein said targeting agent is selected from the group consisting of oligonucleotides, antibodies and ligands for cell surface receptors.

DETD Another aspect of the invention (**Composition** AH) is directed to a conjugate according to **Composition** AF, wherein the immunomodulatory moiety is selected from the group consisting of peptides and carbohydrates.

DETD Another aspect of the invention (**Composition** AI) is directed to a conjugate according to **Composition** AF, wherein the immunomodulatory moiety is a peptide incorporating a sequence derived from an immunogenic protein of viral or bacterial. . .

DETD Another aspect of the invention (**Composition** AJ) is directed to a conjugate according to **Composition** AF, wherein the immunomodulatory moiety elicits a cytotoxic lymphocyte response.

DETD Another aspect of the invention (**Composition** AK) is directed to a conjugate according to **Composition** AJ, wherein the immunomodulatory moiety is cyclosporin A or interleukin-6.

DETD administering an amount effective to modulate immune response of a conjugate in accordance with **Composition** AF.

DETD . . . thrombin activity was studied using a consensus-related

sequence 7-mer, 5' GGTTGGG 3', or a control 7-mer with the same base **composition** but different sequence (5' GGGGGTT 3'). Clotting times were measured using the timer apparatus as above. The thrombin clotting time. . .

DETD . . . protein and
RLF1 protein)
early gene products (including SMLF1, MRF1, ALF2, HRF1,
ribonucleotide reductase, thymidine kinase [XLF1])
virus-encoded glycoproteins
lipopolysaccharides (from gram negative or grain positive
bacteria)
botulinum toxin
diphtheria toxin
cholera toxin
endotoxin
D. Intracellular Targets (proteins/lipids/Enzymes
Lipids
fatty acids
glycerides
glycerylethers
phospholipids
sphingolipids
steroids
fat soluble vitamins
glycolipid
phospholipids
lecithins
phosphatidic acids (cephalins)
sphingomyelin
plasmalogens
phosphatidyl inositol
phosphatidyl choline
phosphatidyl serine
phosphatidyl inositol
diphosphatidyl glycerol
oleic
palmitic
stearic acids
linoleic acid
acylcoenzyme A
phosphoglyceride
phosphitidate
retinoic acid
retinoids
lipoprotein. . . Other Compounds
2-phosphoglycerate
3-hydroxy acyl-CoA
3-phospho-5-pyrophosphomevalonate
3-phosphoglycerate
3-phosphohydroxypyruvate
3-phosphoserine
5-alpha-dihydrotestosterone
5-phospho-beta-ribosylamine
5-phosphoribosyl 1-pyrophosphate
5-phospho-alpha-ribosyl-1-pyrophosphate
5-phosphoribosyl-4-carboxamide-5-aminoimidazole
6-benzylaminopurine
17-hydroxyprogesterone
acetominophen
aceyt-coenzyme A
acetylcholine
acetylsalicylic acid
adenine
adenosine

ADP
aflatoxin B1
aflatoxin G1
aflatoxin M1
aldosterone
allantoin
allodeoxycholic acid
allopurinol
alpha ketoglutarate
alpha,beta-dihydroxy-beta-methylvalerate
alpha-aceto-alpha-hydroxybutyrate
alpha-amino-beta-ketoadipate
alpha-bungarotoxin
alpha-carotine
alpha-keto-beta-methylvalerate
alpha-ketoglutarate
alpha-ketobutyrate
alpha-ketoglutarate
amiloride
aminopterin
AMP
amylopectin
amylose
anti-diuretic hormone
antipyrine
arachidic acid
arachidonic acid
arecoline
arginine
argininosuccinate
ascorbic acid
aspartate semialdehyde
aspartyl phosphate
ATP
atropine
bacitracine
benztropine
beta-caratine
betamethazone
bilirubin
biliverdin
biotin
carbachol
carbamoyl phosphate
carboline
carnitine
CDP
cholesterol
cholic acid
chorismic acid
cis aconitate
citrate
citrulline
CMP
cocaine
codeine
Coenzyme Q
coenzyme A
corticosterone
cortisol
cortisone
coumarin
creatine
creatinine

CTP
cyanocobalamin
cyclic AMP
cyclic CMP
cyclic GMP
cyclic TMP
cystathionine
cytnidine
cytochrome
D-Erythrose
D-Fructose
D-Galactosamine
D-glucose
D-Glucuronic acid
dADP
dAMP
dATP
dCDP
dCMP
dCTP
delta-4-androstenedione
deoxyadenosyl cobalamin
deoxycholic acid
dGDP
dGMP
dGTP
dihydroorotate
dihydroxyphenylalanine
diphosphoglycerate
dopanane
dTDP
dTMP
dTTP
dUDP
dUMP
dUTP
eosinophil chemotactic factor of anaaphyaxis-A
epinephrine
estriol
esdone
ethynylestrdiol
FAD
farnesyl pyrophosphate
fatty Acyl-s-CoA
ferrodoxin
FMN
FMNH2
folic acid
fructose 2,6-diphosphate
fructose
fructose 1,6-diphosphate
fructose 6-phosphate
Fructosel,6-diphosphate
fumarate
galactose
galactose
GalNAC
gama-aminolevulinate
gamma-carotene
gastric inhibitory protein
gaunidinoacetate
GDP
gentamycin
glucosamine

glucosamine 6-phosphate
glucose
glucose 1,6-diphosphate
glucose 1-phosphate
glucose 6-phosphate
Glutamate
glutamate semialdehyde
glutaryl-CoA
glutathione
glyceraldehyde 3-phosphate
glycerol 1-phosphate
glychocholate
glycine
glyoxylate
GMP
GTP
guanine
hemichohne
histamine
homogentisate
homoserine
hydrocortisone
hydroxyproline
indole
inosine
inositol
inositol phosphate
intermediate molecular weight eosinophil chemotactic
factor. . .

L16 ANSWER 14 OF 50 USPATFULL
ACCESSION NUMBER: 1998:6916 USPATFULL
TITLE: Photoactivatable chemiluminescent matrices
INVENTOR(S): Pease, John S., Los Altos, CA, United States
Kirakossian, Hrair, San Jose, CA, United States
Wagner, Daniel B., Sunnyvale, CA, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syntex (U.S.A.) Inc., San Jose, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5709994		19980120
APPLICATION INFO.:	US 1995-470862		19950606 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-923069, filed on 31 Jul 1992
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Myers, Carla J.
LEGAL REPRESENTATIVE: Finnegan, Henderson, Farabow, Garrett & Dunner
NUMBER OF CLAIMS: 74
EXEMPLARY CLAIM: 1
LINE COUNT: 3237
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB . . . presence of the analyte and determining whether the sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties. Upon activation of the photosensitizer property singlet oxygen is generated and activates the chemiluminescent. . .
SUMM . . . in a fluidic system, (c) wear in a mechanical part or (d) emission of light. The method comprises irradiating a **composition** arising from or subject to the condition. The **composition** comprises a non-particulate solid matrix or a particulate matrix having incorporated therein (a) a photosensitizer

capable upon irradiation of generating. . .

SUMM . . . aspect of the present invention concerns a method for generating delayed luminescence. The method comprises the step of irradiating a **composition** comprising a non-particulate, solid matrix or particulate solid or fluid matrix having incorporated therein (1) a photosensitizer capable upon irradiation. . .

SUMM . . . presence of the analyte and determining whether the sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties such that upon activation of the photosensitizer property singlet oxygen is generated and activates. . .

SUMM . . . of containing said analyte, (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both photosensitizer and chemiluminescent properties such that upon activation of the photosensitizer property singlet oxygen is generated and activates. . .

SUMM Another embodiment of the invention is a **composition** comprising a non-particulate solid matrix or particulate solid or fluid having incorporated therein a photosensitizer capable upon activation of generating. . .

SUMM Another **composition** in accordance with the invention comprises a particle, either solid or fluid, having incorporated therein a photosensitizer capable of generating. . .

SUMM Another embodiment of the invention is a **composition** comprising fluid particles selected from the group consisting of oil droplets, liposomes and emulsions having incorporated therein a photosensitizer capable. . .

SUMM Another embodiment of the present invention is a method for calibrating light intensity emitted by a luminescent **composition**, The method comprises the steps of (a) combining in a medium a luminescent **composition** capable of emitting light upon irradiation and one of the above compositions of the invention, wherein one of the compositions. . . for light emission substantially greater than the decay time for the other, (b) irradiating the medium to activate the luminescent **composition** and the **composition** of the invention, (c) measuring the intensity of light emitted during the decay of the activated **composition** having the shorter decay time, (d) measuring the intensity of light emitted after the measuring of step (c) and after at least partial decay of the activated **composition** having the shorter decay time, and (e) comparing the intensity of the light emitted during the decay of the activated **composition** having the shorter decay time with the intensity of light emitted in step (d) to provide for internal calibration. Steps b and c may be repeated one or more times prior to step d. In one embodiment the activated **composition** of **composition** of the invention has the shorter decay time. Another embodiment of the present invention is a kit comprising one of. . .

SUMM . . . lifetime of the luminescent decay is determined by a number of factors including the structure of the chemiluminescent compound, the **composition** of the solid material or the particle, the temperature and the presence of activators that enhance the rate of decomposition. . .

SUMM . . . gas. Application of tracers to detect leaks is well-known in the art. In general, about 10.sup.-14 -10.sup.-2 % of a **composition** of the invention is dispersed into the liquid or gas. Next, the fluid is irradiated with light to activate the. . .

SUMM . . . reaction of singlet oxygen with the chemiluminescent compound to be sufficiently stable so that luminescence will not occur until the **composition** is heated. Preferably, for these applications the **composition** is in the form of a film. The compositions may also be used to calibrate light sources and photometric devices.. . .

SUMM . . . where they can be used as a label or as part of a labeled reagent. For the most part the **composition** will have a member of a specific binding pair (sbp) bound to its surface. The sbp member

may be capable. . .

SUMM Where the molecule to be detected involves a cell, the cell can be labeled with a particulate **composition** of the invention. For example, the **composition** of the invention can include an sbp member complementary to an sbp member on the surface of the cell. The. . .

SUMM The present compositions can be utilized for internal calibration in luminescent assays. By including particles of the **composition** in an assay medium in which luminescence is produced by irradiating the medium, the **composition** produces an emission that can be detectably different from that produced in the assay. This difference can be the result. . .

SUMM . . . a fluorescence immunoassay the fluorescence intensity is measured first. Irradiation of the medium is discontinued and luminescence emanating from the **composition** of the invention is measured to provide an accurate internal reference of light intensity, detector sensitivity and sample interference. The. . . the measurement. Following the final cycle, the intensity of light which will now be emanating primarily from the present particulate **composition** can be independently measured because the decay times for the present particulate compositions are much longer. The residual light intensity. . . can be ratioed against the residual intensity of the present particulate compositions to provide for internal calibration. Conversely the present **composition** decay times could be shorter than the '490 **composition** decay times and the same procedure could be used for calibration except that the rapidly decaying light intensity would serve. . .

SUMM An assay for an analyte may be accomplished by separating a particulate **composition** of the invention used as a label, to which has become bound an analyte or an sbp member whose presence is indicative of the presence of an analyte, from unbound **composition**. Either the separated bound or unbound fraction is treated to activate the photosensitizer, usually by irradiation with light, and the. . .

SUMM Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

SUMM . . . Spore-forming Bacilli

	Phialophora jeanselmei
Bacillus anthracis	Microsporum gypseum
Bacillus subtilis	Trichophyton mentagrophytes
Bacillus megaterium	Keratinomyces ajelloi
Bacillus cereus	Microsporum canis
Anaerobic Spore-forming Bacilli	
	Trichophyton rubrum
Clostridium **botulinum**	Microsporum adouini
Clostridium tetani	Viruses
Clostridium perfringens	Adenoviruses
Clostridium novyi	Herpes Viruses
Clostridium septicum	Herpes simplex
Clostridium histolyticum	Varicella (Chicken pox)
Clostridium tertium	Herpes Zoster (Shingles)

Clostridium. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeins, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids; . . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and metabolites of the above.

SUMM The next group of drugs is miscellaneous individual drugs which include

methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

SUMM Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

SUMM . . . the most part, when a linking group is bound to the photosensitizer, the photochemically activatable chemiluminescent compound or a particulate **composition** of the invention will have a non-oxocarbonyl group including nitrogen and sulfur analogs, a phosphate group, an amino group, alkylating. . .

SUMM . . . the above functionalities can also be utilized as attaching groups, which permit attachment of an sbp member to a particulate **composition** comprised of the photosensitizer and chemiluminescent compound.

SUMM . . . chemical reagents is required to activate the present compositions and the photosensitizer and the chemiluminescent compound are found within one **composition**.

SUMM . . . case these compounds will preferably be hydrophobic to reduce their ability to dissociate from the particle. In general the particle **composition** is chosen so as to favor association of the photosensitizer and the chemiluminescent compound with the particle.

SUMM . . . CC can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

SUMM . . . containing an analyte and (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both a photosensitizer and a CC. Conditions are chosen such that an sbp member complex is formed in relation. . .

SUMM Another factor that allows for control of the time to luminescence is the **composition** or the particle. In general, when the particle is composed of a non-polar material in which the CC is dissolved. . .

SUMM . . . formed in relation to the presence of the analyte and determining whether the sbp member complex has formed. A particulate **composition** of the invention is employed as a label to assist in the determination. An sbp member complex involving the label reagent is formed in relation to the presence of analyte in the medium. The **composition** is then irradiated with light and light energy from the chemiluminescent compound is measured such as, for example, by visual. . .

SUMM Another aspect of the present invention is a **composition** comprising a solid matrix having incorporated therein a photosensitizer capable upon activation of generating singlet oxygen and a chemiluminescent compound. . . compound can be covalently linked to the matrix or can be associated with the matrix with no covalent bounds. The **composition** can comprise one or a plurality of distinct chemiluminescent compounds and one or a plurality of distinct photosensitizers and can. . . energy from the chemiluminescent compound. The distinct chemiluminescent compounds may differ by differing rates of activation by singlet oxygen. The **composition** may also comprise an activator that may or may not be fluorescent and that enhances the decay of an activated chemiluminescent compound. The **composition** can further comprise a member of a specific binding pair (sbp) bound thereto wherein the **composition** is usually particulate.

SUMM Another aspect of the present invention is a **composition** comprising a particle having incorporated therein a photosensitizer capable of generating singlet oxygen and a chemiluminescent compound

capable of being. . .

SUMM . . . be combined in one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises a **composition** comprising a suspendible particle having associated therewith a chemiluminescent compound and a photosensitizer, the particle having an sbp member bound. . .

CLM What is claimed is:

1. A method for determining the presence or absence of an analyte, said method comprising: irradiating a **composition** suspected of containing the analyte, said **composition** comprising a non-particulate solid matrix or a particulate matrix, said matrix having incorporated therein (1) a photosensitizer that upon irradiation. . .

8. A method for generating delayed luminescence, said method comprising the step of irradiating a **composition** comprising a solid or particulate matrix having incorporated therein (1) a photosensitizer that upon irradiation generates singlet oxygen, and (2). . .

. . . the presence of said analyte; determining whether said sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties such that upon activation of said photosensitizer property singlet oxygen is generated and activates. . .

14. The method of claim 13, wherein said single **composition** is a solid matrix or a particle having incorporated therein a photosensitizer that upon irradiation generates singlet oxygen and a. . .

. . . of containing said analyte, (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both photosensitizer and chemiluminescent properties such that upon activation of said photosensitizer property singlet oxygen is generated and activates. . .

20. The method of claim 19, wherein said single **composition** is a solid matrix or a particle having incorporated therein a photosensitizer that upon irradiation generates singlet oxygen and a. . .

30. A **composition** comprising a solid matrix having incorporated therein a photosensitizer that upon activation generates singlet oxygen and a chemiluminescent compound activatable. . .

31. The **composition** of claim 30 wherein said photosensitizer is bound to said chemiluminescent compound.

32. The **composition** of claim 30 wherein at least one of said photosensitizer and said chemiluminescent compound is covalently linked to said matrix.

. . .

33. The **composition** of claim 30 comprising a plurality of distinct chemiluminescent compounds.

34. The **composition** of claim 33 wherein said distinct chemiluminescent compounds differ by differing rates of decay of emission following activation by singlet. . .

35. The **composition** of claim 30 wherein said photosensitizer and said chemiluminescent compound are covalently linked to said matrix.

36. The **composition** of claim 30 which comprises an activator that enhances the decay of activated chemiluminescent compound.

37. The **composition** of claim 30 comprising a member of a specific binding pair (sbp) bound thereto.

38. The **composition** of claim 37 wherein said sbp member is selected from the group consisting of ligands, receptors, polynucleotides and polynucleotide binding. . .

39. The **composition** of claim 30 wherein said photosensitizer is a dye selected from the group consisting of methylene blue, rose

bengal, porphyrin,. . .
40. The **composition** of claim 30 wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .
41. The **composition** of claim 30 wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-methyl acridans, enol ethers and enamines.
. . .
42. The **composition** of claim 30 wherein said solid matrix is a particle having as average diameter of about 20 nanometers to 20. . .
43. A **composition** comprising a particle having incorporated therein a photosensitizer that generates singlet oxygen and a chemiluminescent compound activatable by the singlet. . .
44. The **composition** of claim 43 wherein said molecule is a member of a specific binding pair.

45. The **composition** of claim 43 wherein said photosensitizer is covalently bound to said chemiluminescent compound.

46. The **composition** of claim 44 wherein said sbp member is selected from the group consisting of ligands, receptors, polynucleotides and polynucleotide binding. . .
47. The **composition** of claim 43 wherein said photosensitizer is a dye selected from the group consisting of methylene blue, rose bengal, porphyrins,. . .
48. The **composition** of claim 43 wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .
49. The **composition** of claim 43 wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-methyl acridans, enol ethers and enamines.
. . .
50. The **composition** of claim 43 wherein said photosensitizer and said chemiluminescent compound are dissolved in said particle.

51. The **composition** of claim 43 comprising a plurality of distinct chemiluminescent compounds.

52. The **composition** of claim 51 wherein said distinct chemiluminescent compounds differ by differing rates of decay after activation by singlet oxygen.

53. The **composition** of claim 43 which comprises an activator that enhances the decay of activated chemiluminescent compounds.

54. A **composition** comprising fluid particles selected from the group consisting of oil droplets, liposomes and emulsions having incorporated therein a photosensitizer that. . .
55. The **composition** of claim 54 wherein said photosensitizer is bound to said chemiluminescent compound.

56. The **composition** of claim 54 wherein at least one of said photosensitizer and said chemiluminescent compound is covalently linked to said matrix.
. . .
57. The **composition** of claim 54 comprising a plurality of distinct chemiluminescent compounds.

58. The **composition** of claim 57 wherein said distinct chemiluminescent compounds differ by differing rates of decay of emission following activation by singlet. . .
59. The **composition** of claim 54 wherein said photosensitizer and said chemiluminescent compound are covalently linked to molecules comprising said fluid particles.

60. The **composition** of claim 54 which comprises an activator that enhances the decay of activated chemiluminescent compound.

61. The **composition** of claim 54 comprising a member of a specific binding pair (sbp) bound thereto.

62. The **composition** of claim 61 wherein said sbp member is selected from the group consisting of ligands, receptors, polynucleotides and polynucleotide binding. . .
63. The **composition** of claim 54 wherein said photosensitizer is a dye selected from the group consisting of methylene blue, rose bengal, porphyrin,. . .
64. The **composition** of claim 54 wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .
65. The **composition** of claim 54 wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-methyl acridans, enol ethers and enamines.
. . .
66. A kit comprising: (a) the **composition** of claim 36 and (b) a member of a specific binding pair.

67. A kit comprising: (a) the **composition** of claim 43 and (b) a member of a specific binding pair.

68. A kit comprising: (a) the **composition** of claim 55 and (b) a member of a specific binding pair.

. . . for determining a leak in a fluidic system, said method comprising: introducing into a fluid in the fluidic system a **composition** comprising a non-particulate solid matrix or a particulate matrix, said matrix having incorporated therein (1) a photosensitizer that upon irradiation. . .
71. A method for determining wear in a mechanical pad comprising: incorporating into the mechanical part a **composition** comprising a non-particulate solid matrix or a particulate matrix, said matrix having incorporated therein (1) a photosensitizer that upon irradiation. . .
73. A method for detecting the emission of light comprising: irradiating a **composition** comprising a non-particulate solid matrix or a particulate matrix, said matrix having incorporated therein (1) a photosensitizer that upon irradiation. . .

L16 ANSWER 15 OF 50 USPATFULL

ACCESSION NUMBER:	97:104285 USPATFULL
TITLE:	Method of stabilizing enzyme conjugates
INVENTOR(S):	Skold, Carl N., Mountain View, CA, United States Henson, Margaret, Mountain View, CA, United States Houts, Thomas Michael, Mountain View, CA, United States Gibbons, Ian, Portola Valley, CA, United States
PATENT ASSIGNEE(S):	Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5686253		19971111
APPLICATION INFO.:	US 1995-450744		19950525 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1990-616115, filed on 20 Nov 1990, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Saunders, David		
LEGAL REPRESENTATIVE:	Leitereg, Theodore J.		

NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
LINE COUNT: 1905
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM In developing an enzyme conjugate for use as an assay reagent stability is an important consideration. An enzyme conjugate **composition** used in an assay is usually prepared well in advance of the time the assay procedure is performed. Storage of. . . be subjected to wide temperature variations and other conditions which promote the loss of enzyme activity. Accordingly, an enzyme conjugate **composition** which exhibits substantially improved stability characteristics by comparison with known compositions is a useful improvement in the assay field.

SUMM Another aspect of the invention concerns a **composition** comprising an immune complex comprised of (1) a conjugate of an enzyme and a member of a specific binding pair and (2) an antibody for the enzyme where the antibody does not substantially inhibit the enzyme. The **composition** can further include a second member of a specific binding pair where the second member is usually capable of binding. . .

SUMM Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzoyl ecgonine, their derivatives and metabolites, ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, and their metabolites.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . Spore-forming Bacilli
Phialophora jeanselmei
Bacillus anthracis
Microsporum gypseum
Bacillus subtilis Trichophyton mentagrophytes
Bacillus megaterium
Keratinomyces ajelloi
Bacillus cereus Microsporum canis
Anaerobic Spore-forming Bacilli
Trichophyton rubrum
Clostridium **botulinum**
Microsporum adouini
Clostridium tetani
Viruses
Clostridium perfringens
Adenoviruses
Clostridium novyi Herpes Viruses
Clostridium septicum
Herpes simplex
Clostridium histolyticum
Varicella (Chicken pox)
Clostridium tertium
Herpes Zoster (Shinglee)
Clostridium. . .

SUMM Polynucleotide--a compound or **composition** which is a polymeric

nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

SUMM Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

SUMM In accordance with the present invention, a **composition** is employed in place of enzyme labeled sbp member. The **composition** comprises enzyme labeled sbp member and antibody for the enzyme that does not substantially inhibit the activity of the enzyme. . .

SUMM . . . and a second sbp member complementary to the analyte can be bound to the support. In any such instance, a **composition** in accordance with the present invention can be substituted for the enzyme conjugate reagent. Exemplary of heterogeneous immunoassays are the. . .

SUMM . . . one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises as one reagent a **composition** in accordance with the invention. As mentioned above, for homogeneous immunoassays the preferred enzymes of the enzyme conjugate are dehydrogenases,. . .

CLM What is claimed is:

28. A **composition** comprising (1) a conjugate of an enzyme and a member of a specific binding pair (sbp) having a molecular weight. . . the sbp member of said conjugate to bind to its complementary sbp member, wherein said antibody is present in said **composition** in a molar amount that is 5-fold or greater than the molar amount of said conjugate, said amount being sufficient. . .

29. The **composition** of claim 28 wherein said enzyme is a dehydrogenase.

30. The **composition** of claim 28 wherein said enzyme is a glucose-6-phosphate dehydrogenase.

31. The **composition** of claim 28 wherein said enzyme is malate dehydrogenase.

32. The **composition** of claim 28 wherein said enzyme is horseradish peroxidase.

33. The **composition** of claim 28 wherein said enzyme is glucose oxidase.

34. The **composition** of claim 28 wherein said member is a hapten.

35. The **composition** of claim 28 wherein said antibody for said enzyme is a monoclonal antibody.

36. A kit comprising in packaged combination (a) **composition** comprised of (1) a conjugate of an enzyme and a member of a specific binding pair (sbp) having a molecular. . . inhibit the ability of said member to bind to its complementary sbp member, wherein said antibody is present in said **composition** in a molar amount that is 5-fold or greater than the molar amount of said conjugate, said amount being sufficient. . .

L16 ANSWER 16 OF 50 USPATFULL
ACCESSION NUMBER: 97:88865 USPATFULL
TITLE: Methods of use for and kits containing chemiluminescent compounds
INVENTOR(S): Singh, Sharat, San Jose, CA, United States
Singh, Rajendra, Mountain View, CA, United States
Meneghini, Frank, Keene, NH, United States
Ullman, Edwin F., Atherton, CA, United States

PATENT ASSIGNEE(S): Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5672478		19970930
APPLICATION INFO.:	US 1996-661846		19960611 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-373678, filed on 17 Jan 1995, now patented, Pat. No. US 5545834 which is a continuation of Ser. No. US 1992-916453, filed on 20 Jul 1992, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Marschel, Ardin H.
ASSISTANT EXAMINER: Riley, Jezia
LEGAL REPRESENTATIVE: Leitereg, Theodore J.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1892
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD . . . group
Hemophilus influenzae
H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pastourella tulareusis
Brucellae
Brucalla melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Baclllus subtilis
Bacillus megaterium
Bacillus cerous
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septic
Clostridium histolyticum
Clostridium tertium
Clostridium bifermontans
Clostrldium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycotes (fungus-like bacteria)

Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polynucleotide: a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD . . . context of the present invention, a ligand conjugated to a chemiluminescent label of this invention, is a ligand-label conjugate. A **composition** which is described as comprising subunit A conjugated to subunit B is a **composition** wherein subunit A is bound to subunit B.

DETD One embodiment of the present invention pertains to a chemiluminescent **composition** comprising a chemiluminescent compound of this invention in a pH 6-10 aqueous solution containing hydrogen peroxide or a means for. . . a hapten or an antibody, in the manner described above. Compound (I) is particularly suited for use in such a **composition**. If peroxide is to be detected, it will usually be desirable to have a relatively high concentration of the chemiluminescent. . .

DETD Another embodiment of the present invention is a light emitting chemical **composition** comprised of hydrogen peroxide and a chemiluminescent compound of this invention, for example, Compound (II). It is usually desirable to. . .

DETD . . . compound can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD One such kit comprises in packaged combination (1) a **composition** comprising a chemiluminescent compound of this invention, for example Compound (I), having bound thereto a specific binding pair member and. . . of hydrogen peroxide, or an analyte that modulates the formation of hydrogen peroxide, and comprises in packaged combination (1) a **composition** comprising the compound A--L--Q described herein and (2) any ancillary reagents required to produce hydrogen peroxide from said analyte when. . .

CLM What is claimed is:

33. A kit comprising in packaged combination (1) a **composition** comprising the compound of claim 1 having bound thereto a specific binding pair (sbp) member and (2) hydrogen peroxide or. . . . . detection of hydrogen peroxide or an analyte that modulates the formation of hydrogen peroxide, comprising in packaged combination (1) a **composition** comprising the label reagent of claim 6 and (2) any ancillary reagents required to produce hydrogen peroxide from said

analyte. . .

L16 ANSWER 17 OF 50 USPATFULL
ACCESSION NUMBER: 97:49519 USPATFULL
TITLE: Heterogeneous assay using a pendulous drop
INVENTOR(S): Meltzer, Robert J., Kirkland, WA, United States
PATENT ASSIGNEE(S): Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5637467		19970610
APPLICATION INFO.:	US 1995-412636		19950329 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-960032, filed on 13 Oct 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Housel, James C.
ASSISTANT EXAMINER: King, Theresa
LEGAL REPRESENTATIVE: Precivale, Shelley G., Kaku, Janet K., Clarke, Pauline Ann
NUMBER OF CLAIMS: 55
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1529
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .
DETD The microorganisms that are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
DETD Clostridium **botulinum**
DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .
DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.
DETD The next group of drugs is miscellaneous individual drugs, which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.
DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .
DETD Polynucleotide: a compound or **composition** that is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

L16 ANSWER 18 OF 50 USPATFULL
ACCESSION NUMBER: 97:29389 USPATFULL
TITLE: Method of calibration with photoactivatable chemiluminescent matrices
INVENTOR(S): Pease, John S., Los Altos, CA, United States
Kirakossian, Hrair, San Jose, CA, United States
Wagner, Daniel B., Sunnyvale, CA, United States

	Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5618732		19970408
APPLICATION INFO.:	US 1995-434617		19950504 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1992-923069, filed on 31 Jul 1992		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Snay, Jeffrey		
LEGAL REPRESENTATIVE:	Leitereg, Theodore J.		
NUMBER OF CLAIMS:	3		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2936		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . presence of the analyte and determining whether the sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties. Upon activation of the photosensitizer property singlet oxygen is generated and activates the chemiluminescent. . .

SUMM . . . in a fluidic system, (c) wear in a mechanical part or (d) emission of light. The method comprises irradiating a **composition** arising from or subject to the condition. The **composition** comprises a non-particulate solid matrix or a particulate matrix having incorporated therein (a) a photosensitizer capable upon irradiation of generating. . .

SUMM . . . aspect of the present invention concerns a method for generating delayed luminescence. The method comprises the step of irradiating a **composition** comprising a non-particulate, solid matrix or particulate solid or fluid matrix having incorporated therein (1) a photosensitizer capable upon irradiation. . .

SUMM . . . presence of the analyte and determining whether the sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties such that upon activation of the photosensitizer property singlet oxygen is generated and activates. . .

SUMM . . . of containing said analyte, (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both photosensitizer and chemiluminescent properties such that upon activation of the photosensitizer property singlet oxygen is generated and activates. . .

SUMM Another embodiment of the invention is a **composition** comprising a non-particulate solid matrix or particulate solid or fluid having incorporated therein a photosensitizer capable upon activation of generating. . .

SUMM Another **composition** in accordance with the invention comprises a particle, either solid or fluid, having incorporated therein a photosensitizer capable of generating. . .

SUMM Another embodiment of the invention is a **composition** comprising fluid particles selected from the group consisting of oil droplets, liposomes and emulsions having incorporated therein a photosensitizer capable. . .

SUMM Another embodiment of the present invention is a method for calibrating light intensity emitted by a luminescent **composition**, The method comprises the steps of (a) combining in a medium a luminescent **composition** capable of emitting light upon irradiation and one of the above compositions of the invention, wherein one of the compositions. . . for light emission substantially greater than the decay time for the other, (b) irradiating the medium to activate the luminescent **composition** and the **composition** of the invention, (c) measuring the intensity of light emitted during the decay

of the activated **composition** having the shorter decay time, (d) measuring the intensity of light emitted after the measuring of step (c) and after at least partial decay of the activated **composition** having the shorter decay time, and (e) comparing the intensity of the light emitted during the decay of the activated **composition** having the shorter decay time with the intensity of light emitted in step (d) to provide for internal calibration. Steps b and c may be repeated one or more times prior to step d. In one embodiment the activated **composition** of **composition** of the invention has the shorter decay time. Another embodiment of the present invention is a kit comprising one of. . .

DETD . . . lifetime of the luminescent decay is determined by a number of factors including the structure of the chemiluminescent compound, the **composition** of the solid material or the particle, the temperature and the presence of activators that enhance the rate of decomposition. . .

DETD . . . gas. Application of tracers to detect leaks is well-known in the art. In general, about 10.sup.-14 -10.sup.-2 % of a **composition** of the invention is dispersed into the liquid or gas. Next, the fluid is irradiated with light to activate the. . .

DETD . . . reaction of singlet oxygen with the chemiluminescent compound to be sufficiently stable so that luminescence will not occur until the **composition** is heated. Preferably, for these applications the **composition** is in the form of a film. The compositions may also be used to calibrate light sources and photometric devices.. . .

DETD . . . where they can be used as a label or as part of a labeled reagent. For the most part the **composition** will have a member of a specific binding pair (sbp) bound to its surface. The sbp member may be capable. . .

DETD Where the molecule to be detected involves a cell, the cell can be labeled with a particulate **composition** of the invention. For example, the **composition** of the invention can include an sbp member complementary to an sbp member on the surface of the cell. The. . .

DETD The present compositions can be utilized for internal calibration in luminescent assays. By including particles of the **composition** in an assay medium in which luminescence is produced by irradiating the medium, the **composition** produces an emission that can be detectably different from that produced in the assay. This difference can be the result. . .

DETD . . . a fluorescence immunoassay the fluorescence intensity is measured first. Irradiation of the medium is discontinued and luminescence emanating from the **composition** of the invention is measured to provide an accurate internal reference of light intensity, detector sensitivity and sample interference. The. . . the measurement. Following the final cycle, the intensity of light which will now be emanating primarily from the present particulate **composition** can be independently measured because the decay times for the present particulate compositions are much longer. The residual light intensity. . . can be ratioed against the residual intensity of the present particulate compositions to provide for internal calibration. Conversely the present **composition** decay times could be shorter than the '490 **composition** decay times and the same procedure could be used for calibration except that the rapidly decaying light intensity would serve. . .

DETD An assay for an analyte may be accomplished by separating a particulate **composition** of the invention used as a label, to which has become bound an analyte or an sbp member whose presence is indicative of the presence of an analyte, from unbound **composition**. Either the separated bound or unbound fraction is treated to activate the photosensitizer, usually by irradiation with light, and the. . .

DETD Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

DETD . . . Spore-forming Bacilli
Phialophora jeanselmei
Bacillus anthracis Microsporum gypseum
Bacillus subtilis Trichophyton mentagrophytes
Bacillus megaterium
Keratinomyces ajelloi
Bacillus cereus Microsporum canis
Anaerobic Spore-forming Bacilli
Trichophyton rubrum
Clostridium **botulinum**
Microsporum adouini
Clostridium tetani Viruses
Clostridium perfringens
Adenoviruses
Clostridium novyi Herpes Viruses
Clostridium septicum
Herpes simplex
Clostridium histolyticum
Varicella (Chicken pox)
Clostridium tertium
Herpes Zoster (Shingles)
Clostridium. . .

DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeins, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD . . . the most part, when a linking group is bound to the photosensitizer, the photochemically activatable chemiluminescent compound or a particulate **composition** of the invention will have a non-oxocarbonyl group including nitrogen and sulfur analogs, a phosphate group, an amino group, alkylating. . .

DETD . . . the above functionalities can also be utilized as attaching groups, which permit attachment of an sbp member to a particulate **composition** comprised of the photosensitizer and chemiluminescent compound.

DETD . . . chemical reagents is required to activate the present compositions and the photosensitizer and the chemiluminescent compound are found within one **composition**.

DETD . . . case these compounds will preferably be hydrophobic to reduce their ability to dissociate from the particle. In general the particle **composition** is chosen so as to favor association of the photosensitizer and the chemiluminescent compound with the particle.

DETD . . . CC can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD . . . containing an analyte and (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both a photosensitizer and a CC. Conditions are chosen such that an sbp member complex is formed in relation. . .

DETD Another factor that allows for control of the time to luminescence is the **composition** or the particle. In general, when the particle is composed of a non-polar material in which the CC is dissolved. . .

DETD . . . formed in relation to the presence of the analyte and determining whether the sbp member complex has formed. A particulate **composition** of the invention is employed as a label to assist in the determination. An sbp member complex involving the label reagent is formed in relation to the presence of analyte in the medium. The **composition** is then irradiated with light and light energy from the chemiluminescent compound is measured such as, for example, by visual. . .

DETD Another aspect of the present invention is a **composition** comprising a solid matrix having incorporated therein a photosensitizer capable upon activation of generating singlet oxygen and a chemiluminescent compound. . . compound can be covalently linked to the matrix or can be associated with the matrix with no covalent bounds. The **composition** can comprise one or a plurality of distinct chemiluminescent compounds and one or a plurality of distinct photosensitizers and can. . . energy from the chemiluminescent compound. The distinct chemiluminescent compounds may differ by differing rates of activation by singlet oxygen. The **composition** may also comprise an activator that may or may not be fluorescent and that enhances the decay of an activated chemiluminescent compound. The **composition** can further comprise a member of a specific binding pair (sbp) bound thereto wherein the **composition** is usually particulate.

DETD Another aspect of the present invention is a **composition** comprising a particle having incorporated therein a photosensitizer capable of generating singlet oxygen and a chemiluminescent compound capable of being. . .

DETD . . . be combined in one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises a **composition** comprising a suspendible particle having associated therewith a chemiluminescent compound and a photosensitizer, the particle having an sbp member bound. . .

CLM What is claimed is:

1. A method for calibrating light intensity emitted by a luminescent **composition**, said method comprising the steps of: (a) combining in a medium a luminescent **composition** capable of emitting light upon irradiation and a **composition** comprising a solid matrix having incorporated therein a photosensitizer capable upon activation of generating singlet oxygen and a chemiluminescent compound. . . for light emission substantially greater than the decay time for the other, (b) irradiating said medium to activate said luminescent **composition** and said **composition**, (c) measuring the intensity of light emitted during the decay of the activated **composition** having the shorter decay time, (d) measuring the intensity of light emitted after said measuring of step (c) and after at least partial decay of the activated **composition** having the shorter decay time, and (e) comparing the intensity of the light emitted during the decay of the activated **composition** having the shorter decay time with the intensity of light emitted in step (d) to provide for internal calibration.

3. The method of claim 1 wherein said activated **composition** comprising said solid material has the shorter decay time.

L16 ANSWER 19 OF 50 USPATFULL
ACCESSION NUMBER: 96:73076 USPATFULL

TITLE: Chemiluminescent compounds and methods of use
INVENTOR(S): Singh, Sharat, San Jose, CA, United States
Singh, Rajendra, Mountain View, CA, United States
Meneghini, Frank, Keene, NH, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5545834		19960813
APPLICATION INFO.:	US 1995-373678		19950117 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-916453, filed on 20 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Datlow, Philip I.
LEGAL REPRESENTATIVE: Precivale, Shelley G., Leitereg, Theodore J.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1932
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD Clostridium **botulinum**

DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polynucleotide: a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD . . . context of the present invention, a ligand conjugated to a chemiluminescent label of this invention, is a ligand-label conjugate. A **composition** which is described as comprising subunit A conjugated to subunit B is a **composition** wherein subunit A is bound to subunit B.

DETD One embodiment of the present invention pertains to a chemiluminescent **composition** comprising a chemiluminescent compound of this invention in a pH 6-10 aqueous solution containing hydrogen peroxide or a means for. . . a hapten or an antibody, in the manner described above. Compound (I) is particularly suited for use in such a **composition**. If peroxide is to be detected, it will usually be

desirable to have a relatively high concentration of the chemiluminescent. . .

DETD Another embodiment of the present invention is a light emitting chemical **composition** comprised of hydrogen peroxide and a chemiluminescent compound of this invention, for example, Compound (II). It is usually desirable to. . .

DETD . . . compound can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD One such kit comprises in packaged combination (1) a **composition** comprising a chemiluminescent compound of this invention, for example Compound (I), having bound thereto a specific binding pair member and. . . of hydrogen peroxide or an analyte that modulates the formation of hydrogen peroxide, and comprises in packaged combination (1) a **composition** comprising the compound A-L-Q described herein and (2) any ancillary reagents required to produce hydrogen peroxide from said analyte when. . .

CLM What is claimed is:

4. A chemiluminescent **composition** comprised of the compound of claim 1 in a pH 6-10 aqueous solution containing hydrogen peroxide.

5. A light emitting chemical **composition** comprising hydrogen peroxide and a compound having the following formula: ##STR34## wherein: X' is selected from the group consisting of. . .

6. The **composition** of claim 5 wherein said compound is chemiluminescent and wherein said **composition** further comprises a catalyst to enhance chemiluminescence.

9. The **composition** of claim 5 wherein said compound has the formula: ##STR37##

L16 ANSWER 20 OF 50 USPATFULL

ACCESSION NUMBER:	94:73204 USPATFULL
TITLE:	Assay method utilizing photoactivated chemiluminescent label
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Kirakossian, Hrair, San Jose, CA, United States Pease, John S., Los Altos, CA, United States Daniloff, Yuri, Mountain View, CA, United States Wagner, Daniel B., Sunnyvale, CA, United States
PATENT ASSIGNEE(S):	Snytex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5340716		19940823	
APPLICATION INFO.:	US 1991-718490		19910620	(7)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Wax, Robert A.
ASSISTANT EXAMINER:	Schmickel, David
LEGAL REPRESENTATIVE:	Leitereg, Theodore J.
NUMBER OF CLAIMS:	86
EXEMPLARY CLAIM:	1
LINE COUNT:	2698

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Another embodiment of the invention is a **composition** comprising a photochemically activatable chemiluminescent compound bound to an sbp member.

SUMM Another embodiment of the invention is a kit comprising the above **composition**.

SUMM Analyte--the compound or **composition** to be detected. The

analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

SUMM . . . Spore-forming Bacilli
Phialophora jeanselmei
Bacillus anthracis Microsporum gypseum
Bacillus subtilis Trichophyton
mentagrophytes
Bacillus megaterium Keratinomyces ajelloi
Bacillus cereus Microsporum canis
Anaerobic Spore-forming Bacilli
Trichophyton rubrum
Clostridium **botulinum**
Microsporum adouini
Clostridium tetani Viruses
Clostridium perfringens
Adenoviruses
Clostridium novyi Herpes Viruses
Clostridium septicum Herpes simplex
Clostridium histolyticum
Varicella (Chicken pox)
Clostridium tertium Herpes Zoster (Shingles)
Clostridium. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and metabolites of the above.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

SUMM Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

SUMM . . . both compounds to associate with the same particle. This possibly can be further reduced by utilizing particles of only one **composition** that are associated with either the photosensitizer or chemiluminescent compound or by using two types of particles that differ in **composition** so as to favor association of the photosensitizer with one type of particle and association of the chemiluminescent compound with. . .

SUMM . . . photosensitizer can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

SUMM . . . combined in one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises (1) a **composition** comprising a PACC bound to an sbp member. The kit can also include one or more additional sbp member reagents. . .

CLM What is claimed is:
72. A **composition** comprising a photochemically activated chemiluminescent compound (PACC) associated with a member of a specific binding pair.

73. The **composition** of claim 72 wherein said PACC contains an olefin group.

74. The **composition** of claim 72 wherein said PACC contains an olefin group and one or more electron donating substitutents in conjugation with. . .
75. The **composition** of claim 72 wherein said PACC is selected from the group consisting of 9-alkyline-N-alkyl acridans, enolethers, enamines, and 9-alkylidene xanthenes.
. . .
76. The **composition** of claim 72 wherein said sbp member is selected from the group consisting of receptors, ligands, and polynucleotides.

77. A kit comprising in packaged combination: (1) a **composition** comprising a photochemically activatable chemiluminescent compound (PACC), having bound thereto a specific binding pair (sbp) member, and (2) a photosensitizer which is not in said **composition**.

L16 ANSWER 21 OF 50 USPATFULL
ACCESSION NUMBER: 94:5790 USPATFULL
TITLE: Method of separation employing magnetic particles and second medium
INVENTOR(S): Vorpahl, John, Livermore, CA, United States
PATENT ASSIGNEE(S): Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5279936		19940118	
APPLICATION INFO.:	US 1989-455550		19891222	(7)

DISCLAIMER DATE: 20070619
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Nucker, Christine M.
ASSISTANT EXAMINER: Preston, D. R.
LEGAL REPRESENTATIVE: Leitereg, Theodore J., Bosse, Mark L.
NUMBER OF CLAIMS: 80
EXEMPLARY CLAIM: 1
LINE COUNT: 1535
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Component of interest (CI)--the compound or **composition** to be separated. The component of interest can be non-particulate or particulate. Non-particulate CI can be comprised of a member. . .
DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzoyl ecgonine, their derivatives and metabolites, ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .
DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, and their metabolites.
DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.
DETD . . . Spore-forming Bacilli
Phialophora jeanselmei
Bacillus anthracis Microsporum gypseum

Bacillus subtilis Trichophyton mentagrophytes
Bacillus megaterium
                   Keratinomyces ajelloi
Bacillus cereus   Microsporum canis
Anaerobic Spore-forming Bacilli
                   Trichophyton rubrum
Clostridium **botulinum**
                   Microsporum adouini
Clostridium tetani Viruses
Clostridium perfringens
                   Adenoviruses
Clostridium novyi Herpes Viruses
Clostridium septicum
                   Herpes simplex
Clostridium histolyticum
                   Varicella (Chicken pox)
Clostridium tertium
                   Herpes Zoster (Shingles)
Clostridium. . .

DETD Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polyionic reagent--a compound, **composition**, or material, either inorganic or organic, naturally occurring or synthetic, having at least two of the same charge, either polyanionic. . .

DETD Releasing agent--a compound, **composition**, or material, either naturally occurring or synthetic, organic or inorganic, capable of reversing the non-specific binding between, i.e., dissociating, particulate. . .

DETD The invention further comprises a **composition** comprising (1) a first liquid medium containing magnetic particles to which are bound a component of interest (CI) and in. . . therewith (2) a second liquid medium having a different density and/or viscosity or immiscibility with the first liquid medium. The **composition** may further comprise a polyionic reagent of opposite charge to the magnetic particles. Alternatively, in the **composition** of the invention the magnetic particles can have a CI bound to an sbp member bound thereto.

CLM What is claimed is:

51. A **composition** comprising: (a) a first liquid medium containing magnetic particles wherein said magnetic particles are selected from the group consisting of. . .

52. The **composition** of claim 51 wherein said PBM is bound to said magnetic particles by means of charge-charge interactions.

53. The **composition** of claim 51 wherein said PBM is a cell or a microorganism.

L16 ANSWER 22 OF 50 USPATFULL

ACCESSION NUMBER:	92:100755 USPATFULL
TITLE:	Method and apparatus for optically detecting presence of immunological components
INVENTOR(S):	Joseph, Jose P., Menlo Park, CA, United States Itoh, Kiminori, Tokyo, Japan
PATENT ASSIGNEE(S):	Teknekron Sensor Development Corporation, Menlo Park, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5169599		19921208	
APPLICATION INFO.:	US 1990-576359		19900830	(7)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			

PRIMARY EXAMINER: Johnston, Jill A.
LEGAL REPRESENTATIVE: Limbach & Limbach
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 730

DETD Analyte is used throughout this specification to refer to the compound or **composition** to be detected and measured, which is a mip and may be a ligand, which is mono- or polyepitopic, that. . .

DETD Receptor (antiligand)--any macromolecular compound or **composition** capable of recognizing (having an enhanced binding affinity to) a particular spatial or determinant site. Illustrative receptors include naturally occurring. . .

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD . . . group
Hemophilus influenzae,
H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Antinomyces naeslundii
Nocardia asteroides
Nocardia. . .

DETD . . . pollutants, and the like. Included are the alkaloids: morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, and their metabolites.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol,griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 23 OF 50 USPATFULL

ACCESSION NUMBER: 88:62445 USPATFULL

TITLE: Fluorescent conjugates bound to a support

INVENTOR(S): Khanna, Pyare, Mountain View, CA, United States
Ullman, Edwin F., Atherton, CA, United States

PATENT ASSIGNEE(S): Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4774191		19880927
APPLICATION INFO.:	US 1986-826177		19860205 (6)

RELATED APPLN. INFO.: Division of Ser. No. US 1984-664121, filed on 23 Oct 1984, now patented, Pat. No. US 4588697 which is a division of Ser. No. US 1982-399506, filed on 19 Jul 1982, now patented, Pat. No. US 4481136 which is a division of Ser. No. US 1979-73158, filed on 7 Sep 1979, now patented, Pat. No. US 4351760

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Warden, Robert J.

ASSISTANT EXAMINER: Benson, Robert

LEGAL REPRESENTATIVE: Leitereg, Theodore J., Barrett, Carole F.

NUMBER OF CLAIMS: 2

EXEMPLARY CLAIM: 1

LINE COUNT: 1246

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum

Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

CLM What is claimed is:
1. A **composition** of matter consisting of a conjugate bonded to a Support, and of the formula: ##STR9## wherein: n.sup.3 is 1 to. . .
2. A **composition** of matter according to claim 1, wherein support is a polysaccharide.

L16 ANSWER 24 OF 50 USPATFULL

ACCESSION NUMBER:	87:20611 USPATFULL
TITLE:	Fluorescent protein binding assays with unsymmetrical fluorescein derivatives
INVENTOR(S):	Khanna, Pyare, San Jose, CA, United States Colvin, Warren, Redwood City, CA, United States
PATENT ASSIGNEE(S):	Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4652531		19870324
APPLICATION INFO.:	US 1984-587085		19840307 (6)
RELATED APPLN. INFO.:	Division of Ser. No. US 1981-340031, filed on 3 Mar 1981, now patented, Pat. No. US 4439356		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Marantz, Sidney		
LEGAL REPRESENTATIVE:	Rowland, Bertram I., Leitereg, Theodore J., Barrett, Carole F.		
NUMBER OF CLAIMS:	4		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1088		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . group

Hemophilus influenzae,
H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their

metabolites and derivatives.

L16 ANSWER 25 OF 50 USPATFULL

ACCESSION NUMBER:	87:18722 USPATFULL
TITLE:	Energy absorbing particle quenching in light emitting competitive protein binding assays
INVENTOR(S):	Liu, Yen-Ping, Santa Clara, CA, United States Ullman, Edwin F., Atherton, CA, United States Becker, Martin J., Palo Alto, CA, United States
PATENT ASSIGNEE(S):	Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4650770		19870317
APPLICATION INFO.:	US 1983-559555		19831207 (6)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1981-258176, filed on 27 Apr 1981, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Kepplinger, Esther M.
ASSISTANT EXAMINER:	Jay, Jeremy
LEGAL REPRESENTATIVE:	Leitereg, Theodore J., Rowland, Bertram I.
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1
LINE COUNT:	1292

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor (anti-ligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, i.e., determinant or epitopic site. Illustrative of receptors. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM The particles may be homogeneous or non-homogeneous, isotropic or anisotropic, in that the particle **composition** or quenching functionalities may be uniformly or non-uniformly dispersed, usually uniformly dispersed. The particles should provide sufficient quenching, so that. . .

DETD . . . series of tubes were prepared by adding in each tube 50 .mu.l of a 1/8th dilution of a carbon particle **composition** to 1 ml of 0.1% ovalbumin/PBS/NaN.sub.3 buffer. A series of solutions of

different concentrations of human IgG were prepared which. . .

L16 ANSWER 26 OF 50 USPATFULL
ACCESSION NUMBER: 86:28171 USPATFULL
TITLE: Method for performing fluorescent protein binding assay employing novel alkyl substituted fluorescent compounds and conjugates
INVENTOR(S): Khanna, Pyare, Mountain View, CA, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4588697		19860513
APPLICATION INFO.:	US 1984-664121		19841023 (6)

RELATED APPLN. INFO.: Division of Ser. No. US 1982-399506, filed on 19 Jul 1982, now patented, Pat. No. US 4481136 which is a division of Ser. No. US 1979-73158, filed on 7 Sep 1979, now patented, Pat. No. US 4351760
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Nucker, Christine M.
LEGAL REPRESENTATIVE: Barrett, Carole F., Leitereg, Theodore J., Rowland, Bertram I.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 1437
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
SUMM Clostridium **botulinum**
SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .
SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.
SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.
SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 27 OF 50 USPATFULL
ACCESSION NUMBER: 85:11772 USPATFULL
TITLE: Charge effects in enzyme immunoassays
INVENTOR(S): Gibbons, Ian, Menlo Park, CA, United States
Rowley, Gerald L., Cupertino, CA, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 4501692	19850226
APPLICATION INFO.:	US 1982-259629	19820501 (6)
RELATED APPLN. INFO.:	Division of Ser. No. US 1979-61099, filed on 26 Jul 1979, now patented, Pat. No. US 4287300	
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Kight, John	
ASSISTANT EXAMINER:	Draper, Garnette D.	
LEGAL REPRESENTATIVE:	Rowland, Bertram I., Leitereg, Theodore J.	
NUMBER OF CLAIMS:	1	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1551	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . weight % of the total protein as the antibody of interest. When preparing reagents which involve reactions with the antibody **composition**, the presence of the large amount of contaminant must be taken into account.

SUMM . . . system label will frequently be added prior to the charged member. The two reagents may be provided as a single **composition** or as separate compositions, depending upon the nature of the protocol.

SUMM Analyte-the compound or **composition** to be measured, which may be a ligand, a single or plurality of compounds which share at least one common. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. determinant or epitopic site. Illustrative receptors include. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)

Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .
SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .
SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.
SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.
SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 28 OF 50 USPATFULL
ACCESSION NUMBER: 84:62202 USPATFULL
TITLE: Alkyl substituted fluorescent compounds and conjugates
INVENTOR(S): Khanna, Pyare, Mountain View, CA, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4481136		19841106
APPLICATION INFO.:	US 1982-399506		19820719 (6)

RELATED APPLN. INFO.: Division of Ser. No. US 1979-73158, filed on 7 Sep 1979, now patented, Pat. No. US 4351760
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kight, John
ASSISTANT EXAMINER: Nutter, Nathan M.
LEGAL REPRESENTATIVE: Rowland, Bertram I., Leitereg, Theodore J.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 1275
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
SUMM . . . H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis

Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli -Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethrophan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 29 OF 50 USPATFULL

ACCESSION NUMBER:	84:17157 USPATFULL
TITLE:	Unsymmetrical fluorescein derivatives
INVENTOR(S):	Khanna, Pyare, San Jose, CA, United States Colvin, Warren, Redwood City, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4439356		19840327	
APPLICATION INFO.:	US 1981-240031		19810303	(6)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Kight, III, John			
ASSISTANT EXAMINER:	Nutter, Nathan M.			
LEGAL REPRESENTATIVE:	Rowland, Bertram I.			
NUMBER OF CLAIMS:	22			

EXEMPLARY CLAIM: 1
LINE COUNT: 1231
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
SUMM Clostridium **botulinum**
SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .
SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.
SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.
SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 30 OF 50 USPATFULL
ACCESSION NUMBER: 83:27797 USPATFULL
TITLE: Test strip kits in immunoassays and compositions therein
INVENTOR(S): Litman, David J., Cupertino, CA, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4391904		19830705	
APPLICATION INFO.:	US 1981-255022		19810417	(6)

DISCLAIMER DATE: 19981110
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1979-106620, filed on 26 Dec 1979, now patented, Pat. No. US 4299916
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wiseman, Thomas G.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1,6
LINE COUNT: 2355
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic, usually antigenic or haptenic, a single or. . .
DETD Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic or determinant site. Illustrative receptors include. . .
DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
DETD . . . H. hemophilus
H. aegypticus

H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia. . .

DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, ctecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

DETD The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . will involve aralkylamine structures, which may or may not be a part of a heterocyclic structure, e.g. alkaloids, phenobarbitol, dilantin, **epinephrine**, L-dopa, etc. While there is some similarity in structure, the compounds vary widely as to activity.

DETD . . . hydrophilic, i.e. polar or non-polar, preferably hydrophilic, may be coated with a thin mono- or polymolecular layer of a different **composition** or uncoated, may be a single material or a plurality of materials, particularly as laminates or fibers, may be woven,. . .

DETD . . . 10 .mu.l of 3.9 mg/ml catalase and incubating for 60 min at RT with a developer solution of the following **composition**: 50 mM

bicine, pH 8.0, 200 mM KCl, 2 mg/ml BSA, 50 mM .beta.-D-glucose and 0.1 mg/ml 4-Cl-1-naphthol. The difference. . .

L16 ANSWER 31 OF 50 USPATFULL

ACCESSION NUMBER:	83:9021 USPATFULL
TITLE:	Macromolecular environment control in specific receptor assays
INVENTOR(S):	Litman, David J., Palo Alto, CA, United States Harel, Zvi, Stanford, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4374925		19830222	
APPLICATION INFO.:	US 1981-232777		19810209	(6)
DISCLAIMER DATE:	19980623			
RELATED APPLN. INFO.:	Division of Ser. No. US 1978-964099, filed on 24 Nov 1978, now patented, Pat. No. US 4275149, issued on 23 Jun 1981			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Wiseman, Thomas G.			
LEGAL REPRESENTATIVE:	Rowland, Bertram I.			
NUMBER OF CLAIMS:	4			
EXEMPLARY CLAIM:	1			
LINE COUNT:	2405			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaoilds, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 32 OF 50 USPATFULL

ACCESSION NUMBER:	82:62955 USPATFULL
TITLE:	Concentrating zone method in heterogeneous immunoassays

INVENTOR(S):	Tom, Henry K., La Honda, CA, United States Rowley, Gerald L., Cupertino, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4366241		19821228	
APPLICATION INFO.:	US 1980-176177		19800807	(6)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Wiseman, Thomas G.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	34
EXEMPLARY CLAIM:	1,15,22
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:	2456

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Analyte--the compound or **composition** to be measured, which is a mip and may be a ligand, which is mono- or polyepitopic, that is, having. . .

DETD (b) Receptor (antiligand)--any macromolecular compound or **composition** capable of recognizing (having an enhanced binding affinity to) a particular spatial and polar organization of a molecule, i.e. epitopic. . .

DETD . . . solutes diffusing to and away from a layer immersed in a liquid. Thus the layer encounters a continuously changing solution **composition** as solute becomes bound to the layer or dissolves into the liquid. In the subject invention, the mip containing layer in contact with the solution continuously contacts substantially the same solution **composition** as the solution diffuses through the layer. Thus, the concentrations of solutes in the solution in the mip containing layer. . .

DETD . . . manner in which the time for diffusion of the solutions through the immunosorbing zone may be controlled will involve the **composition**, construction, size and shape of the immunosorbing and liquid absorbing zones, the temperature, the solvent, and the like. In view. . .

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD Clostridium **botulinum**

DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

DETD The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

CLM What is claimed is:

. . . said assay device, wherein said immunosorbing zone is immersed in

said sample solution; flowing said sample solution of substantially constant **composition** through said immunosorbing zone; whereby said solutions migrate through said immunosorbing zone into said liquid absorbing zone resulting in an. . .

. . . precursor, wherein said immunosorbing zone is substantially completely immersed in said sample solution; flowing said sample solution having substantially constant **composition** through said immunosorbing zone; whereby said solutions migrate through said immunosorbing zone into said liquid absorbing zone and said signal. . .

L16 ANSWER 33 OF 50 USPATFULL

ACCESSION NUMBER:	82:47270 USPATFULL
TITLE:	Novel alkyl substituted fluorescent compounds and polyamino acid conjugates
INVENTOR(S):	Khanna, Pyare, Mountain View, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4351760		19820928	
APPLICATION INFO.:	US 1979-73158		19790907	(6)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Schain, Howard E.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	7
EXEMPLARY CLAIM:	1
LINE COUNT:	1390

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

CLM What is claimed is:

5. A **composition** of matter consisting of a conjugate bonded to a Support, and of the formula: ##STR10## wherein: n.sup.3 is 1 to. . .

6. A **composition** of matter according to claim 5, wherein said support is a polysaccharide.

7. A **composition** of matter according to any of claims 5 and 6, wherein A.sup.2 is a poly(amino acid) of from about 2,000. . .

L16 ANSWER 34 OF 50 USPATFULL
ACCESSION NUMBER: 82:21571 USPATFULL
TITLE: Enzyme-aminoglycoside conjugates
INVENTOR(S): Rowley, Gerald L., San Jose, CA, United States
Leung, Danton, Campbell, CA, United States
Singh, Prithipal, Santa Clara, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4328311		19820504
APPLICATION INFO.:	US 1980-125713		19800228 (6)

RELATED APPLN. INFO.: Division of Ser. No. US 1978-876772, filed on 10 Feb 1978, now patented, Pat. No. US 4220722, issued on 2 Sep 1980
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shapiro, Lionel M.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 1430
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . of interest, but the analyte having the protective groups. This may result in substantially reducing the specificity of the antibody **composition** for the analyte of interest.
SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
SUMM Clostridium **botulinum**
SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecogonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .
SUMM . . . aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, methyldopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.
SUMM . . . miscellaneous individual drugs which include methadone, phenoxybenzamine and related haloalkylamines, tolamol, sotalol, guanethide, meprobamate, serotonin, meperidine, chlorcyclazine, chlorpheniramine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, methotrexate, aminopterin, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 35 OF 50 USPATFULL
ACCESSION NUMBER: 82:11141 USPATFULL
TITLE: Novel ether substituted fluorescein polyamino acid compounds as fluorescers and quenchers
INVENTOR(S): Khanna, Pyare, Mountain View, CA, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4318846		19820309

APPLICATION INFO.: US 1979-73163 19790907 (6)
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Schain, Howard E.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
LINE COUNT: 1641
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . efficient response to such reagent. Furthermore, where the fluorescer is to be used in the presence of serum or other **composition**, which is in itself fluorescent, it is desirable that the fluorescer absorb energy in a substantially different range from that. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazolyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their

metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 36 OF 50 USPATFULL

ACCESSION NUMBER:	81:47741 USPATFULL
TITLE:	Charge effects in enzyme immunoassays
INVENTOR(S):	Gibbons, Ian, Menlo Park, CA, United States Rowley, Gerald L., Cupertino, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4287300		19810901	
APPLICATION INFO.:	US 1979-61099		19790726	(6)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Wiseman, Thomas G.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	15
EXEMPLARY CLAIM:	1,7
LINE COUNT:	1855

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . weight % of the total protein as the antibody of interest. When preparing reagents which involve reactions with the antibody **composition**, the presence of the large amount of contaminant must be taken into account.

SUMM . . . system label will frequently be added prior to the charged member. The two reagents may be provided as a single **composition** or as separate compositions, depending upon the nature of the protocol.

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, a single or plurality of compounds which share at least one common. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. determinant or epitopic site. Illustrative receptors include. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline,

nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

CLM What is claimed is:

7. A **composition** useful for the immunoassay of claim 1 comprising, a macromolecular charged substrate or coenzyme and modified members of a specific. . .

8. An assay **composition** according to claim 7, wherein said charged member is polycarboxyl substituted antiligand and said signal labeled member is .beta.-galactosidase substituted. . .

9. An assay **composition** according to claim 7, wherein said macromolecular charged substrate is a positively charged substrate for said .beta.-galactosidase having a plurality. . .

10. An assay **composition** according to claim 7, wherein said charged member is a polyphenolic substituted antiligand and said signal labeled member is .beta.-galactosidase. . .

11. An assay **composition** according to claim 10, wherein said charged macromolecular substrate is a positively charged substrate for said .beta.-galactosidase having a plurality. . .

L16 ANSWER 37 OF 50 USPATFULL

ACCESSION NUMBER: 81:40928 USPATFULL

TITLE: Double antibody for enhanced sensitivity in immunoassay

INVENTOR(S): Zuk, Robert F., San Francisco, CA, United States
Gibbons, Ian, Menlo Park, CA, United States
Rowley, Gerald L., Cupertino, CA, United States
Ullman, Edwin F., Atherton, CA, United States

PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4281061		19810728	
APPLICATION INFO.:	US 1979-61542		19790727	(6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wiseman, Thomas G.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 1497
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Method and **composition** are provided for determining small amounts of organic compounds in a wide variety of media by employing an organic receptor. . .

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic (antigenic determinants) or haptenic, a single or. . .

SUMM Receptor--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae

Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

CLM What is claimed is:

15. An assay **composition** for use in the method of claim 1 comprising in combination in relative predetermined amounts to substantially optimize the signal. . .

16. An assay **composition** according to claim 15, wherein labeled ligand is enzyme bonded to ligand and said macromolecular member is an enzyme substrate.

. . .

17. An assay **composition** according to claim 15, wherein labeled ligand is fluorescer bonded to ligand and said macromolecular member is antifluorescer.

L16 ANSWER 38 OF 50 USPATFULL
ACCESSION NUMBER: 81:34595 USPATFULL

TITLE: Macromolecular environment control in specific receptor assays

INVENTOR(S): Litman, David J., Palo Alto, CA, United States
Harel, Zvi, Stanford, CA, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4275149		19810623	
APPLICATION INFO.:	US 1978-964099		19781124	(5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wiseman, Thomas G.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1,19,46
LINE COUNT: 2543
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

CLM What is claimed is:
46. A **composition** comprising a discrete porous particle of a size in the range of about 500 nm to 100.mu. to which is. . .

L16 ANSWER 39 OF 50 USPATFULL

ACCESSION NUMBER:	81:31786 USPATFULL		
TITLE:	Purification of reagents by disulfide immobilization		
INVENTOR(S):	Schwarzberg, Moshe, Hastings on Hudson, NY, United States		
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4272506		19810609
APPLICATION INFO.:	US 1979-71526		19790831 (6)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Fagelson, Anna P.		
LEGAL REPRESENTATIVE:	Rowland, Bertram I.		
NUMBER OF CLAIMS:	10		
EXEMPLARY CLAIM:	1,9		
LINE COUNT:	1010		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . cleavable under mild conditions to provide a binding pair member-support conjugate. Combining the binding pair member-support conjugate with a labeled **composition** containing the reciprocal member of the binding pair, so that the labeled reciprocal member becomes bound to the support through. . . to provide labeled reagent for immunoassays. In particular, an antibody is linked to a support by disulfide linkage and a **composition** containing the reciprocal antigen to the antibody is labeled with a chromophore, particularly fluorescer. The support is freed of labeled. . .

SUMM . . . mercapto groups with a functionality which allows for reaction with a second mercapto group to produce a disulfide linkage. A **composition** containing one of the members of a specific binding pair--antigen and its homologous antibody--is modified to introduce mercapto groups, if such mercapto groups are not naturally present. The mercapto group containing **composition** is combined with the activated support to provide for the binding of the member of a specific binding pair to the support through disulfide links. A second **composition** having the reciprocal member of the specific binding pair is labeled with labels capable of providing a detectible signal, the labels being in sufficient amount to ultimately insure a desired signal level. The labeled **composition** is then combined with the support **composition**, where the binding pair members bind, so that the labeled member is now bound to the support through the intermediary. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. aegypticus
H. parainfluenzae
Bordetella pertussis

Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Antinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .
SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steriod alkaloids; iminazoyl alkaloids;. . .
SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their matabolites.
SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.
SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procainemide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 40 OF 50 USPATFULL
ACCESSION NUMBER: 81:20553 USPATFULL
TITLE: Fluorescence quenching with immunological pairs in immunoassays
INVENTOR(S): Ullman, Edwin F., Atherton, CA, United States
Schwarzberg, Moshe, Palo Alto, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

NUMBER KIND DATE

PATENT INFORMATION:	US 4261968	19810414
APPLICATION INFO.:	US 1979-37802	19790510 (6)
DISCLAIMER DATE:	19961113	
RELATED APPLN. INFO.:	Division of Ser. No. US 1976-731255, filed on 12 Oct 1976, now patented, Pat. No. US 4174383 which is a continuation of Ser. No. US 1975-591386, filed on 30 Jun 1975, now patented, Pat. No. US 3996345 which is a continuation-in-part of Ser. No. US 1974-497167, filed on 12 Aug 1974, now abandoned	
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Fagelson, Anna P.	
LEGAL REPRESENTATIVE:	Rowland, Bertram I.	
NUMBER OF CLAIMS:	4	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1664	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . to a hub molecule, usually a polymer, in combination with antibody bound to the other of the F-Q pair. The **composition** is irradiated with light at a wavelength, absorbed by the fluorescing molecule and the amount of fluorescence determined. By employing. . .

SUMM One chromophore is introduced into the assay medium covalently bonded to a receptor **composition** which specifically binds to the ligand. The second chromophore can be introduced into the assay medium in different ways: (1) covalently bonded to a receptor **composition** which is the same or different from the receptor **composition** conjugated to the first chromophore, but in both instances specifically binds to the ligand, and in the presence or absence of polyligand; or covalently bonded to ligand analog, where the ligand analog can compete with ligand for the receptor **composition**. The choice of modes of introduction will depend to a significant degree on the number of independent epitopic or haptenic. . .

DETD . . . fluorescer molecule, by accepting the energy which would otherwise be emitted as fluorescent light. As far as the molecule or **composition** to which the chromophores are joined, in most instances, the fluorescer and quencher will be interchangeable, although there will frequently. . .

DETD Receptor **composition**--receptor **composition** is a homogeneous or heterogeneous **composition** capable of specific non-covalent binding to ligand and ligand analog and includes anti-ligand (a **composition** which specifically recognizes the ligand) and a combination of anti-ligand and anti(anti-ligand) (a **composition** which specifically recognizes the anti-ligand).

DETD . . . on the employment of two chromophores which form a fluorescer-quencher pair. One of the chromophores is covalently bonded to a **composition** (receptor) which specifically recognizes or binds to a ligand. The other chromophore is covalently bonded to ligand analog or receptor.. . .

DETD . . . the assay medium: ligand analog-chromophore, poly(ligand analog)-poly(chromophore), poly(ligand analog), one or two receptors and one or two receptor-chromophores. The first **composition** to be considered will be the ligand analog-chromophore.

DETD . . . should also be noted that when antibodies are prepared for a ligand having a plurality of epitopic sites, the receptor **composition** is not homogeneous. That is, the receptor will have antibodies which recognize different epitopic sites. In referring to receptor, it. . .

DETD . . . the nucleus molecule be water soluble, in most instances, it will be desirable. In any event, the nucleus molecule or **composition** will be capable of stable dispersion in an aqueous medium. Secondly, the nucleus molecule should not absorb light at the. . .

DETD The next group of alkaloids are the **cocaine** alkaloids, which

includes, particularly as metabolites, benzoyl ecgonine and ecgonine.

DETD The alkaloids of primary interest are those which come within the category of drugs of abuse, such as morphine, **cocaine**, mescaline, and lysergic acid, which may be analyzed for the compound or its metabolite, depending on the physiological fluid which. . .

DETD Drugs of interest because of their physiological properties are those which are referred to as catecholamines. Among the catecholamines are **epinephrine**, ephedrine, L-dopa, and norepinephrine.

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD Clostridium **botulinum**

DETD . . . be a complex protein mixture, containing antibody for the ligand, as well as other antibodies and proteins. When the antibody **composition** is labeled with chromophore, a substantial proportion of the chromophore will be bound to protein other than the antibody for. . .

DETD . . . chromophore, particularly quencher, is conjugated to anti(anti-ligand) to provide anti(anti-ligand)-chromophore, which is employed in conjunction with anti-ligand as a receptor **composition** for ligand. In this manner, one can bind a larger number of quencher molecules to the ligand, enhancing the opportunity. . .

L16 ANSWER 41 OF 50 USPATFULL

ACCESSION NUMBER:	81:15079 USPATFULL
TITLE:	Fluorescent scavenger particle immunoassay
INVENTOR(S):	Zuk, Robert F., Mountain View, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4256834		19810317	
APPLICATION INFO.:	US 1979-28640		19790409	(6)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Wiseman, Thomas G.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	23
EXEMPLARY CLAIM:	1,8,10
LINE COUNT:	1746

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. determinant or epitopic site. Illustrative receptors include. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes

ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . Disruptor, Model 35, cup horn, 50% pulse, setting 5, for 2 minutes. A total of 10 mg of an antifluorescein **composition** was diluted to 3 ml with PBS pH7.8 (0.05% NaN.sub.3) followed by the addition of 40 .mu.l of .sup.14 C. . .

L16 ANSWER 42 OF 50 USPATFULL

ACCESSION NUMBER: 80:56609 USPATFULL

TITLE: Reagents and method employing channeling

INVENTOR(S): Maggio, Edward T., Redwood City, CA, United States
Wife, Richard L., Sittingbourne, England
Ullman, Edwin F., Atherton, CA, United States

PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4233402		19801111	
APPLICATION INFO.:	US 1978-893650		19780405	(5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Warden, Robert J.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
LINE COUNT: 1842
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte--The compound or **composition** to be measured, which may be a ligand which is mono-or polyepitopic, antigenic or haptenic, a single or plurality of. . .

SUMM Receptor--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occuring. . .

SUMM . . . covalently joined to a polyfunctionalized hub nucleus, either water soluble or insoluble, the hub nucleus having been indicated previously. This **composition** will be referred to as poly(ligand analog)--polylabel. Desirably, when receptor is bound to ligand in a complex, it will not. . .

SUMM . . . binding site. There can be a plurality of receptors and/or labels bonded together, particularly through a hub nucleus. Such a **composition** will be referred to as polyreceptor-polylabel. Desirably, when ligand is bound to receptor in a complex, there will not be. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitripytline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Another situation is where a **composition** is introduced into the solution which acts as an inhibitor or quencher of the emission of light, either by fluorescence. . .

SUMM . . . evident from the discussion concerned with the reactant label, the signal producing label will vary widely as to its chemical **composition**, function, and nature of interaction with the signal mediator. As with the reactant label, it is desirable that the signal. . .

DETD . . . the following experiments were carried out. A plurality of tubes of different concentrations were prepared. The following table indicates the **composition** of the reaction media.

DETD . . . or antiligand can only be obtained in relatively impure form, one can diminish the background effect when labelling the impure **composition** of ligand or antiligand.

L16 ANSWER 43 OF 50 USPATFULL

ACCESSION NUMBER:	80:56608 USPATFULL		
TITLE:	Antienzyme homogeneous competitive binding assay		
INVENTOR(S):	Yoshida, Robert A., Mountain View, CA, United States Maggio, Edward T., Redwood City, CA, United States		
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4233401		19801111
APPLICATION INFO.:	US 1977-815487		19770714 (5)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Wiseman, Thomas G.		
LEGAL REPRESENTATIVE:	Rowland, Bertram I.		
NUMBER OF CLAIMS:	23		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1473		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Competitive protein binding methods and **composition** combinations for use in the methods are provided for determining an analyte which is a member of an immunological pair. . .

SUMM Analyte-the compound or **composition** to be measured, which may be mono- or polyepitopic, antigenic or haptenic, a single or plurality of compounds which share. . .

SUMM Receptor-any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. an epitopic site, and normally polyvalent i.e.. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of

lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . aminoalkyl benzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

CLM What is claimed is:

20. An assay **composition** for use in the method according to claim 1 comprising enzyme-bound-ligand; ligand receptor and enzyme inhibitor of at least 2,000. . .

21. An assay **composition** according to claim 20, wherein said enzyme inhibitor is antienzyme.

22. An assay **composition** according to claim 20, wherein said enzyme inhibitor is a macromolecular inhibiting enzyme substrate.

23. An assay **composition** for use in the method according to claim 1 for determining antiligand comprising enzyme-bound-ligand and enzyme inhibitor of at least. . .

L16 ANSWER 44 OF 50 USPATFULL

ACCESSION NUMBER: 80:43095 USPATFULL

TITLE: Method for conjugating to polyamino compounds employing haloacyl groups and compositions prepared thereby

INVENTOR(S): Rowley, Gerald L., San Jose, CA, United States
Leung, Danton, Campbell, CA, United States
Singh, Prithiphal, Santa Clara, CA, United States

PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4220722		19800902	
APPLICATION INFO.:	US 1978-876772		19780210	(5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shapiro, Lionel M.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 1446
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of interest, but the analyte having the protective groups. This may result in substantially reducing the specificity of the antibody **composition** for the analyte of interest.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives are metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, methyldopa, **epinephrine**, narceine,

papaverine, their metabolites and derivatives.

SUMM . . . miscellaneous individual drugs which include methadone, phenoxybenzamine and related haloalkylamines, tolamol, sotalol, guanethide, meprobamate, serotonin, merperidine, chlorcyclazine, chlorpheniramine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, methotrexate, aminopterin, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 45 OF 50 USPATFULL
ACCESSION NUMBER: 80:42825 USPATFULL
TITLE: Chemically induced fluorescence immunoassay
INVENTOR(S): Maggio, Edward T., Redwood City, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4220450		19800902	
APPLICATION INFO.:	US 1978-893910		19780405	(5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Marantz, Sidney
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
LINE COUNT: 1336
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of another molecule. For the most part, these compounds are antibodies, which are able to distinguish between the compound or **composition** of interest, and other compounds of analogous structure. By virtue of the binding of the receptor to a labeled ligand,. . .

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM Poly(ligand analog)-label--a **composition** in which a plurality of ligand analogs and one or a plurality of labels are bonded together whereby the ligand. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, detromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

L16 ANSWER 46 OF 50 USPATFULL
ACCESSION NUMBER: 80:29494 USPATFULL
TITLE: Label modified immunoassays
INVENTOR(S): Zuk, Robert F., Mountain View, CA, United States
Maggio, Edward T., Redwood City, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4208479		19800617	
APPLICATION INFO.:	US 1977-815632		19770714	(5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wiseman, Thomas G.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1,8,13,19,22
LINE COUNT: 1595
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . substantial loss of the desired antibodies as well as reduction in the binding constant. That is, those antibodies in the **composition** which have the strongest binding, frequently cannot be removed from the column. Therefore, most methods have avoided labeling antibodies, since. . . .

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Label--a compound or **composition** capable of providing a detectable signal in conjunction with physical activation (or excitation) or chemical reagents and capable of being. . .

SUMM Receptor--Any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. an epitopic site. Illustrative receptors include naturally. . .

SUMM The microorgaisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . aminoalkyl benzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Metabolites related to diseased states include spermine, galactose, phenylpyruvic acid, porphyrin type 1, vanillomandelic acid, **epinephrine** and norepinephrine

SUMM For monoepitopic analytes, it is necessary to prepare a polyepitopic **composition** having a plurality of epitopic sites capable of competing with the ligand. This normally involves modification of the ligand to. . .

SUMM . . . when the receptor is bound to analyte. Third, the label must be

capable of modification by a macromolecular compound or **composition**, so as to modify the signal preferably by diminishing the signal to be measured. In addition, desirable labels are stable,. . .

CLM What is claimed is:

29. An assay **composition** for use in an assay method according to claim 1 which comprises the reagents labeled anti(ligand) and macromolecular modifier in. . .

30. An assay **composition** according to claim 29 wherein said modifier is anti(label).

31. An assay **composition** according to claim 29, including poly(ligand analog).

32. An assay **composition** according to claim 29, including polyepitopic ligand.

33. An assay **composition** for use in a method according to claim 9 which comprises the reagents enzyme labeled anti(ligand) and anti(enzyme) in relative. . .

34. An assay **composition** for use in a method according to claim 33, which comprises the reagents fluorescer labeled anti(ligand) and anti(fluorescer) in relative. . .

35. An assay **composition** for use in a method according to claim 28 which comprises the combined reagents labeled anti(ligand) and Fab anti(label) in. . .

36. An assay **composition** according to claim 35, wherein said label is an enzyme.

37. An assay **composition** according to claim 35, wherein said label is a fluorescer.

L16 ANSWER 47 OF 50 USPATFULL

ACCESSION NUMBER:	80:19816 USPATFULL
TITLE:	Fluorescence quenching with immunological pairs in immunoassays
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Schwarzberg, Moshe, Sunnyvale, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4199559		19800422	
APPLICATION INFO.:	US 1977-766279		19770207	(5)
DISCLAIMER DATE:	19931207			
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1976-731255, filed on 12 Oct 1976, now Defensive Publication No. which is a continuation-in-part of Ser. No. US 1975-591386, filed on 30 Jun 1975, now patented, Pat. No. US 3996345 which is a continuation-in-part of Ser. No. US 1974-497167, filed on 12 Aug 1974, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Marantz, Sidney			
LEGAL REPRESENTATIVE:	Rowland, Bertram I.			
NUMBER OF CLAIMS:	26			
EXEMPLARY CLAIM:	1			
LINE COUNT:	2065			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM One chromophore is introduced into the assay medium covalently bonded to a receptor **composition** which specifically binds to the ligand. The second chromophore can be introduced into the assay medium in

different ways: (1) covalently bonded to a receptor **composition** which is the same or different from the receptor **composition** conjugated to the first chromophore, but in both instances specifically binds to the ligand, and in the presence or absence of polyligand; or covalently bonded to ligand analog, where the ligand analog can compete with ligand for the receptor **composition**. The choice of modes of introduction will depend to a significant degree on the number of independent epitopic or haptenic. . .

SUMM . . . fluorescer molecule, by accepting the energy which would otherwise be emitted as fluorescent light. As far as the molecule or **composition** to which the chromophores are joined, in most instances, the fluorescer and quencher will be interchangeable, although there will frequently. . .

SUMM Receptor **composition**--receptor **composition** is a homogeneous or heterogeneous **composition** capable of specific non-covalent binding to ligand and ligand analog and includes anti-ligand (a **composition** which specifically recognizes the ligand) and a combination of anti-ligand and anti(anti-ligand) (a **composition** which specifically recognizes the anti-ligand).

SUMM . . . on the employment of two chromophores which form a fluorescer-quencher pair. One of the chromophores is covalently bonded to a **composition** (receptor) which specifically recognizes or binds to a ligand. The other chromophore is covalently bonded to ligand analog or receptor.. . .

SUMM . . . the assay medium: ligand analog-chromophore, poly(ligand analog)-poly(chromophore), poly(ligand analog), one or two receptors and one or two receptor-chromophores. The first **composition** to be considered will be the ligand analog-chromophore.

SUMM . . . should also be noted that when antibodies are prepared for a ligand having a plurality of epitopic sites, the receptor **composition** is not homogeneous. That is, the receptor will have antibodies which recognize different epitopic sites. In referring to receptor, it. . .

SUMM . . . the nucleus molecule be water soluble, in most instances, it will be desirable. In any event, the nucleus molecule or **composition** will be capable of stable dispersion in an aqueous medium. Secondly, the nucleus molecule should not absorb light at the. . .

SUMM The next group of alkaloids are the **cocaine** alkaloids, which includes, particularly as metabolites, benzoyl ecgonine and ecgonine.

SUMM The alkaloids of primary interest are those which come within the category of drugs of abuse, such as morphine, **cocaine**, mescaline, and lysergic acid, which may be analyzed for the compound or its metabolite, depending on the physiological fluid which. . .

SUMM Drugs of interest because of their physiological properties are those which are referred to as catecholamines. Among the catecholamines are **epinephrine**, ephedrine, L-dopa, and norepinephrine.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . be a complex protein mixture, containing antibody for the ligand, as well as other antibodies and proteins. When the antibody **composition** is labeled with chromophore, a substantial proportion of the chromophore will be bound to protein other than the antibody for. . .

SUMM . . . chromophore, particularly quencher, is conjugated to anti(anti-ligand) to provide anti(anti-ligand)-chromophore, which is employed in conjunction with anti-ligand as a receptor **composition** for ligand. In this manner, one can bind a larger number of quencher molecules to the ligand, enhancing the opportunity. . .

CLM What is claimed is:

. . . form an assay solution; (1) said unknown; (2) a source of Ch.sub.1 as Ch.sub.1 covalently bound to a first antibody **composition** capable of specific non-covalent binding to said ligand of said sample antibody; (3) a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second antibody **composition** capable of specific non-covalent binding to said ligand or as Ch.sub.2 covalently or non-covalently bound to ligand analog, wherein ligand. . . to the binding sites of said antibodies, with the proviso that when Ch.sub.2 is present bound to said second antibody **composition**, ligand is added to said medium; (B) incubating said assay solution for a sufficient time for at least a portion. . .

. . . form an assay solution; (1) said unknown; (2) a source of Ch.sub.1, as Ch.sub.1 covalently bound to a first receptor **composition** capable of specific non-covalent binding to said ligand; (3) a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second receptor **composition** capable of specific non-covalent binding to said ligand or as Ch.sub.2 covalently or non-covalently bound to ligand analog, wherein ligand. . . be assayed is present in said unknown and said source of Ch.sub.2 is Ch.sub.2 covalently bound to said second receptor **composition**, ligand is added to said medium; (B) incubating said assay solution for a sufficient time for at least a portion. . .

11. A method according to claim 10, wherein ligand is present in said unknown, said first receptor **composition** is a combination of anti-ligand from a first species and anti(first anti-ligand) conjugated to Ch.sub.1, and said second receptor **composition** is anti-ligand from a second species and anti(second anti-ligand) conjugated to Ch.sub.2.

23. A method for determining in an assay solution the presence of an antibody in a sample suspected of containing. . . form an assay solution; (1) said unknown; (2) a source of Ch.sub.1 as Ch.sub.1 covalently bound to a first antibody **composition** capable of specific non-covalent binding to said ligand; (3) a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second antibody **composition** capable of specific non-covalent binding to said ligand; (4) ligand; (B) incubating said assay solution for a sufficient time for. . .

. . . form an assay solution; (1) said unknown; (2) a source of Ch.sub.1 as Ch.sub.1 covalently bound to a first antibody **composition** capable of specific non-covalent binding to said sample antibody; (3) a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second antibody **composition** capable of specific non-covalent binding to said ligand or as Ch.sub.2 covalently or non-covalently bound to ligand analog, wherein ligand. . . to the binding sites of said antibodies, with the proviso that when Ch.sub.2 is present bound to said second antibody **composition**, ligand is added to said medium; (B) incubating said assay solution for a sufficient time for at least a portion. . .

L16 ANSWER 48 OF 50 USPATFULL

ACCESSION NUMBER:	79:45608 USPATFULL
TITLE:	Fluorescence quenching with immunological pairs in immunoassays
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Schwarzberg, Moshe, Palo Alto, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4174384		19791113	
APPLICATION INFO.:	US 1976-731255		19761012	(5)
DISCLAIMER DATE:	19931207			
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1975-591386, filed on 30			

Jun 1975, now patented, Pat. No. US 3996345 which is a continuation-in-part of Ser. No. US 1974-497167, filed on 12 Aug 1974, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Fagelson, Anna P.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
LINE COUNT: 1556
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . to a hub molecule, usually a polymer, in combination with antibody bound to the other of the F-Q pair. The **composition** is irradiated with light at a wavelength, absorbed by the fluorescing molecule and the amount of fluorescence determined. By employing. . .

SUMM One chromophore is introduced into the assay medium covalently bonded to a receptor **composition** which specifically binds to the ligand. The second chromophore can be introduced into the assay medium in different ways: (1) covalently bonded to a receptor **composition** which is the same or different from the receptor **composition** conjugated to the first chromophore, but in both instances specifically binds to the ligand, and in the presence or absence of polyligand; or covalently bonded to ligand analog, where the ligand analog can compete with ligand for the receptor **composition**. The choice of modes of introduction will depend to a significant degree on the number of independent epitopic or haptenic. . .

DETD . . . fluorescer molecule, by accepting the energy which would otherwise be emitted as fluorescent light. As far as the molecule or **composition** to which the chromophores are joined, in most instances, the fluorescer and quencher will be interchangeable, although there will frequently. . .

DETD Receptor **composition**--receptor **composition** is a homogeneous or heterogeneous **composition** capable of specific non-covalent binding to ligand and ligand analog and includes anti-ligand (a **composition** which specifically recognizes the ligand) and a combination of anti-ligand and anti(anti-ligand) (a **composition** which specifically recognizes the anti-ligand).

DETD . . . on the employment of two chromophores which form a fluorescer-quencher pair. One of the chromophores is covalently bonded to a **composition** (receptor) which specifically recognizes or binds to a ligand. The other chromophore is covalently bonded to ligand analog or receptor.. . .

DETD . . . the assay medium: ligand analog-chromophore, poly(ligand analog)-poly(chromophore), poly(ligand analog), one or two receptors and one or two receptor-chromophores. The first **composition** to be considered will be the ligand analog-chromophore.

DETD . . . should also be noted that when antibodies are prepared for a ligand having a plurality of epitopic sites, the receptor **composition** is not homogeneous. That is, the receptor will have antibodies which recognize different epitopic sites. In referring to receptor, it. . .

DETD . . . the nucleus molecule be water soluble, in most instances, it will be desirable. In any event, the nucleus molecule or **composition** will be capable of stable dispersion in an aqueous medium. Secondly, the nucleus molecule should not absorb light at the. . .

DETD The next group of alkaloids are the **cocaine** alkaloids, which includes, particularly as metabolites, benzoyl ecgonine and ecgonine.

DETD The alkaloids of primary interest are those which come within the category of drugs of abuse, such as morphine, **cocaine**, mescaline, and lysergic acid, which may be analyzed for the compound or its metabolite, depending on the physiological fluid which. . .

DETD Drugs of interest because of their physiological properties are those which are referred to as catecholamines. Among the catecholamines are

epinephrine, ephedrine, L-dopa, and norepinephrine.

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD . . . tularеusis

Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium. . .

DETD . . . be a complex protein mixture, containing antibody for the ligand, as well as other antibodies and proteins. When the antibody **composition** is labeled with chorophore, a substantial proportion of the chromophore will be bound to protein other than the antibody for. . .

DETD . . . chromophore, particularly quencher, is conjugated to anti(anti-ligand) to provide anti(anti-ligand)-chromophore, which is employed in conjunction with anti-ligand as a receptor **composition** for ligand. In this manner, one can bind a larger number of quencher molecules to the ligand, enhancing the opportunity. . .

CLM What is claimed is:

1. A **composition** for determining the presence or amount of a ligand comprising two chromophores, which are a fluorescer-quencher pair, the amount of. . .

2. The **composition** of claim 1, which in addition includes one of said chromophores covalently bonded to an antibody to said anti-ligand.

3. The **composition** of claim 1, wherein said ligand is a globulin.

4. The **composition** of claim 1, wherein said ligand is a hapten.

L16 ANSWER 49 OF 50 USPATFULL
ACCESSION NUMBER: 79:30628 USPATFULL
TITLE: Catalyst mediated competitive protein binding assay
INVENTOR(S): Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4160645		19790710

APPLICATION INFO.: US 1977-815636 19770714 (5)
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Marantz, Sidney
LEGAL REPRESENTATIVE: Townsend and Townsend
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
LINE COUNT: 1398
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte -- the compound or **composition** to be measured, which may be a ligand which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor -- any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM Poly(ligand analog)-polylabel -- a **composition** whereby a plurality of ligand analogs and a plurality of labels are bonded to a water soluble polyfunctionalized hub nucleus,. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . aminoalkyl benzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM For monoepitopic ligand analytes, the label may be conjugated to the ligand or a polyepitopic **composition** may be prepared having a plurality of epitopic sites capable of competing with the ligand and capable of being labeled. . .

SUMM The preparation of the polyepitopic **composition** normally involves modification of the ligand to provide for a linking group between a ligand and a hub nucleus, which. . .

L16 ANSWER 50 OF 50 USPATFULL
ACCESSION NUMBER: 76:66499 USPATFULL
TITLE: Fluorescence quenching with immunological pairs in immunoassays
INVENTOR(S): Ullman, Edwin F., Atherton, CA, United States
Schwarzberg, Moshe, Palo Alto, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 3996345		19761207
APPLICATION INFO.:	US 1975-591386		19750630 (5)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1974-497167, filed on 12 Aug 1974, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted

PRIMARY EXAMINER: Wolk, Morris O.
ASSISTANT EXAMINER: Marantz, Sidney
LEGAL REPRESENTATIVE: Townsend and Townsend
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
LINE COUNT: 1790
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . to a hub molecule, usually a polymer, in combination with antibody bound to the other of the F-Q pair. The **composition** is irradiated with light at a wavelength, absorbed by the fluorescing molecule and the amount of fluorescence determined. By employing. . .

SUMM One chromophore is introduced into the assay medium covalently bonded to a receptor **composition** which specifically binds to the ligand. The second chromophore can be introduced into the assay medium in different ways: (1) covalently bonded to a receptor **composition** which is the same or different from the receptor **composition** conjugated to the first chromophore, but in both instances specifically binds to the ligand, and in the presence or absence of polyligand; or covalently bonded to ligand analog, where the ligand analog can compete with ligand for the receptor **composition**. The choice of modes of introduction will depend to a significant degree on the number of independent epitopic or haptenic. . .

SUMM . . . fluorescer molecule, by accepting the energy which would otherwise be emitted as fluorescent light. As far as the molecule or **composition** to which the chromophores are joined, in most instances, the fluorescer and quencher will be interchangeable, although there will frequently. . .

SUMM Receptor **composition**--receptor **composition** is a homogeneous or heterogeneous **composition** capable of specific non-covalent binding to ligand and ligand analog and includes a **composition** which specifically recognizes the ligand(anti-ligand) and a combination of anti-ligand and a **composition** which specifically recognizes the anti-ligand (anti(anti-ligand)).

SUMM The method is predicated on the employment of two chromophores which form a fluorescer-quencher pair. By having a **composition** (receptor) which specifically recognizes or binds to a ligand to which one of the chromophores is covalently bonded, and having. . .

SUMM . . . the assay medium: ligand analog-chromophore, poly(ligand analog)-poly(chromophore), poly(ligand analog), one or two receptors and one or two receptor-chromophores. The first **composition** to be considered will be the ligand analog-chromophore.

SUMM . . . should also be noted that when antibodies are prepared for a ligand having a plurality of epitopic sites, the receptor **composition** is not homogeneous. That is, the receptor will have antibodies which recognize different epitopic sites. In referring to receptor, it. . .

SUMM . . . the nucleus molecule be water soluble, in most instances, it will be desirable. In any event, the nucleus molecule or **composition** will be capable of stable dispersion in an aqueous medium. Secondly, the nucleus molecule should not absorb light at the. . .

SUMM The next group of alkaloids are the **cocaine** alkaloids, which includes, particularly as metabolites, benzoyl ecgonine and ecgonine.

SUMM The alkaloids of primary interest are those which come within the category of drugs of abuse, such as morphine, **cocaine**, mescaline, and lysergic acid, which may be analyzed for the compound or its metabolite, depending on the physiological fluid which. . .

SUMM Drugs of interest because of their physiological properties are those which are referred to as catecholamines. Among the catecholamines are **epinephrine**, ephedrine, L-dopa, and norepinephrine.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest

include:
SUMM . . . H. hemophilus
H. aegypticus
H. paraiufluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .
SUMM . . . be a complex protein mixture, containing antibody for the ligand, as well as other antibodies and proteins. When the antibody **composition** is labeled with chromophore, a substantial proportion of the chromophore will be bound to protein other than the antibody for. . .
CLM What is claimed is:
. . . form an assay solution; 1. said unknown; 2. a source of Ch.sub.1, as Ch.sub.1 covalently bound to a first receptor **composition** capable of specific non-covalent binding to said ligand; 3. a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second receptor **composition** capable of specific non-covalent binding to said ligand or as Ch.sub.2 covalently or non-covalently bound to ligand analog, wherein ligand. . .
3. A method according to claim 1, wherein said first receptor **composition** is a combination of anti-ligand from a first species and anti(first anti-ligand) conjugated to Ch.sub.1, and said second receptor **composition** is anti-ligand from a second species and anti(second anti-ligand) conjugated to Ch.sub.2.

=> d his

(FILE 'HOME' ENTERED AT 11:13:14 ON 27 NOV 2002)

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     FILE 'REGISTRY' ENTERED AT 11:13:29 ON 27 NOV 2002
L1            9 S BOTULINUM TOXIN

     FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT,
     CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL,
     EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF,
     MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 11:16:15 ON 27 NOV 2002
L2        12186 S L1
L3        54772 S BOTULINUM
L4        54912 S L2 OR L3
L5        93949 S LOCAL ANESTHETIC
L6          173 S L4 AND L5
L7        84946 S VASOCONSTRICTOR
L8            2 S L6 AND L7

     FILE 'HOME' ENTERED AT 11:31:29 ON 27 NOV 2002

     FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT,
     CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL,
     EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF,
     MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 11:34:03 ON 27 NOV 2002
L9           27 S L4 AND L7
L10          20 DUP REM L9 (7 DUPLICATES REMOVED)
L11      339813 S EPINEPHRINE OR ADRENALIN OR PHENYLEPHRINE
L12      382445 S BUPIVICAINE OR LIDOCAINE OR MEPIVICAINE OR ?CAINE
L13          76 S L4 AND L11 AND L12
L14          67 DUP REM L13 (9 DUPLICATES REMOVED)
L15     3156465 S COMPOSITION
L16          50 S L14 AND L15

=>
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PRIMARY EXAMINER: Wolk, Morris O.
ASSISTANT EXAMINER: Marantz, Sidney
LEGAL REPRESENTATIVE: Townsend and Townsend
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
LINE COUNT: 1790
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . to a hub molecule, usually a polymer, in combination with antibody bound to the other of the F-Q pair. The **composition** is irradiated with light at a wavelength, absorbed by the fluorescing molecule and the amount of fluorescence determined. By employing. . .

SUMM One chromophore is introduced into the assay medium covalently bonded to a receptor **composition** which specifically binds to the ligand. The second chromophore can be introduced into the assay medium in different ways: (1) covalently bonded to a receptor **composition** which is the same or different from the receptor **composition** conjugated to the first chromophore, but in both instances specifically binds to the ligand, and in the presence or absence of polyligand; or covalently bonded to ligand analog, where the ligand analog can compete with ligand for the receptor **composition**. The choice of modes of introduction will depend to a significant degree on the number of independent epitopic or haptenic. . .

SUMM . . . fluorescer molecule, by accepting the energy which would otherwise be emitted as fluorescent light. As far as the molecule or **composition** to which the chromophores are joined, in most instances, the fluorescer and quencher will be interchangeable, although there will frequently. . .

SUMM Receptor **composition**--receptor **composition** is a homogeneous or heterogeneous **composition** capable of specific non-covalent binding to ligand and ligand analog and includes a **composition** which specifically recognizes the ligand(anti-ligand) and a combination of anti-ligand and a **composition** which specifically recognizes the anti-ligand (anti(anti-ligand)).

SUMM The method is predicated on the employment of two chromophores which form a fluorescer-quencher pair. By having a **composition** (receptor) which specifically recognizes or binds to a ligand to which one of the chromophores is covalently bonded, and having. . .

SUMM . . . the assay medium: ligand analog-chromophore, poly(ligand analog)-poly(chromophore), poly(ligand analog), one or two receptors and one or two receptor-chromophores. The first **composition** to be considered will be the ligand analog-chromophore.

SUMM . . . should also be noted that when antibodies are prepared for a ligand having a plurality of epitopic sites, the receptor **composition** is not homogeneous. That is, the receptor will have antibodies which recognize different epitopic sites. In referring to receptor, it. . .

SUMM . . . the nucleus molecule be water soluble, in most instances, it will be desirable. In any event, the nucleus molecule or **composition** will be capable of stable dispersion in an aqueous medium. Secondly, the nucleus molecule should not absorb light at the. . .

SUMM The next group of alkaloids are the **cocaine** alkaloids, which includes, particularly as metabolites, benzoyl ecgonine and ecgonine.

SUMM The alkaloids of primary interest are those which come within the category of drugs of abuse, such as morphine, **cocaine**, mescaline, and lysergic acid, which may be analyzed for the compound or

its metabolite, depending on the physiological fluid which. . .

SUMM Drugs of interest because of their physiological properties are those which are referred to as catecholamines. Among the catecholamines are **epinephrine**, ephedrine, L-dopa, and norepinephrine.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. hemophilus
H. aegypticus
H. paraiufluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

SUMM . . . In this manner, the ratio of the two common receptors can be carefully controlled and accurately added to the assay **mixture** . The **mixture** can be a dry lyophilized **mixture** or an aqueous, normally buffered (pH 5-10; usually 6.5-8.5) solution of any desired concentration.

SUMM . . . a matter of operability, but rather expedience. In most cases, the receptor is antibody, which will be a complex protein **mixture**, containing antibody for the ligand, as well as other antibodies and proteins. When the antibody **composition** is labeled with chromophore, a substantial proportion of the chromophore will be bound to protein other than the antibody for. . .

SUMM . . . the two conjugated antibodies are combined with the unknown to be assayed, incubated, and the poly(ligand analog) added and the **mixture** further incubated. The times and temperatures previously

indicated are also applicable in this assay.

DETD B. O.sup.3 -aminoethylmorphine (100mg) is dissolved in 5ml of acetone and added to a **mixture** of acetone (20ml), water (5ml), and triethylamine (0.07ml). To this solution is added a solution of FITC (100mg) in acetone. . . with stirring during 15 min. Stirring is continued for an additional 80 min, while adjusting the pH of the reaction **mixture** to 9.5 with drops of dilute triethylamine solution in acetone (1.4ml/10ml acetone). The acetone is then partially removed with a. . .

DETD . . . of 0.sup.3 -carboxymethylmorphine and isobutyl chloroformate (0.1 mmole, large excess) in DMF (2ml) added in the cold (0.degree.), and the **mixture** allowed to react for 3 hours. The gel was filtered and washed sucessively with H.sub.2 O (500ml), 0.1M borate buffer. . .

DETD . . . and then stays stable, and is maintained at 9.0-9.5 if necessary, by careful addition of crystalline potassium carbonate. The reaction **mixture** is then applied to a Sephadex G-25(M) column (1.times.15cm) with 0.01M phosphate buffer pH 7.5 and elution of the first. . .

DETD . . . brought to pH 9.5 with crystalline Na.sub.2 CO.sub.3. TRITC (0.5mg) in acetone (20-30.mu.l) was added at room temperature and the **mixture** stirred for 3 hrs. A precipitate formed which was removed by centrifugation and discarded. The conjugate was then separated twice. . .

DETD . . . increasing amounts of morphine (5-10.mu.l of the standard morphine solutions) for one hour. FLUMO'S' (10.mu.l) was then added and the **mixture** incubated for an additional 1 hour. The final volume of each tube was 3ml. The final concentration of FLUMO'S' was.

.

.

DETD . . . 8.0, containing 1.5.times.10.sup..sup.-6 M bovine gamma-globulin (390-430.mu.l) Codeine in increasing concentrations (1.5.times.10.sup..sup.-3 -1.5.times.10.sup..sup.-6 M) is then added (10-14.mu.l) and the **mixture** incubated at room temperature for 0.5 hr. To each of the tubes is then added 10.mu.l (0.24.mu.g) of the morphine-bovine. . .

DETD . . . bonded to a chromophore and antibody employed which is conjugated to the other member of the fluorescer-quencher pair or the **mixture** of antibodies indicated above employed. The assay is relatively rapid, and depending upon the concentrations, various incubation times are required.. . .

CLM What is claimed is:

. . . form an assay solution; 1. said unknown; 2. a source of Ch.sub.1, as Ch.sub.1 covalently bound to a first receptor **composition** capable of specific non-covalent binding to said ligand; 3. a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second receptor **composition** capable of specific non-covalent binding to said ligand or as Ch.sub.2 covalently or non-covalently bound to ligand analog, wherein ligand. . .

3. A method according to claim 1, wherein said first receptor **composition** is a combination of anti-ligand from a first species and anti(first anti-ligand) conjugated to Ch.sub.1, and said second receptor **composition** is anti-ligand from a second species and anti(second anti-ligand) conjugated to Ch.sub.2.

L2 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2002 ACS
RN 256438-74-1 REGISTRY
CN G protein (guanine nucleotide-binding protein) (human fetal skin gene rac1
isoform Rac1b) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN G protein (guanine nucleotide-binding protein) (human gene Rac1 isoform Rac1b)
CN GenBank AF136373-derived protein GI 4836769
CN GenBank AJ132695-derived protein GI 8574039
CN Phosphatase, guanosine tri- (human gene RAC1 isoenzyme Rac1b)
CN **Ras-related C3 botulinum toxin substrate (human gene Rac1 isoform Rac1b)**
CN Small GTPase rac1b (human fetal skin gene rac1 isoform Rac1b)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, TOXLIT

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2002 ACS
RN 225458-22-0 REGISTRY
CN DNA (human fetal skin gene rac1 G protein (guanine nucleotide-binding protein) isoform Rac1b cDNA) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5043: PN: WO0153836 TABLE: 6 claimed DNA
CN 505: PN: WO0146697 TABLE: 21 claimed DNA
CN 7782: PN: WO0142792 TABLE: 8A-1 claimed DNA
CN DNA (human clone WO0118542_SEQID_1158 ovary tumor-associated protein cDNA)
CN DNA (human fetal skin gene rac1 small GTPase rac1b isoform Rac1b cDNA)
CN DNA (human gene Rac1 G protein (guanine nucleotide-binding protein) isoform Rac1b cDNA)
CN **DNA (human gene Rac1 ras-related C3 botulinum toxin substrate isoform Rac1b cDNA)**
CN GenBank AF136373
CN GenBank AJ132694
CN PN: WO0118542 SEQID: 1158 claimed DNA
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: BIOSIS, CA, CAPLUS, GENBANK, TOXCENTER

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
6 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2002 ACS
RN 127315-80-4 REGISTRY
CN Protein (human clone 5 gene rac2 reduced) (9CI) (CA INDEX NAME)
OTHER NAMES:

CN 13: PN: WO9958669 SEQID: 13 unclaimed protein
CN 44: PN: WO9958670 SEQID: 52 unclaimed protein
CN GenBank Z82188-derived protein GI 5102613
CN **Protein DJ151B14.2 (ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)) (human clone RP1-151B14 gene dJ151B14.1)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, TOXLIT, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2002 ACS
RN 93384-46-4 REGISTRY
CN Botulin D (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Botulin toxin D
CN **Botulinum toxin D**
CN Toxin, botulin, D
MF Unspecified
CI MAN
SR Commission of European Communities
LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, CHEMLIST, CSCHEM, RTECS*, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
77 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
77 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2002 ACS
RN 93384-43-1 REGISTRY
CN Botulin A (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Botox
CN Botulin neurotoxin A
CN Botulin toxin A
CN **Botulinum toxin A**
CN **Botulinum toxin type A**
CN Dysport
CN Oculinum
MF Unspecified
CI MAN
SR Commission of European Communities
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, DRUGNL, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

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*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
             514 REFERENCES IN FILE CA (1967 TO DATE)
              11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             515 REFERENCES IN FILE CAPLUS (1967 TO DATE)


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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      22.12      25.12

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=> file medicine
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.30      25.42

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=> d his

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     FILE 'HOME' ENTERED AT 17:03:52 ON 10 JAN 2002

     FILE 'REGISTRY' ENTERED AT 17:15:31 ON 10 JAN 2002
L1            1 S BOTOX/CN
L2            5 S BOTULINUM TOXIN

     FILE 'HOME' ENTERED AT 17:16:24 ON 10 JAN 2002

     FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT,
     CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL,
     EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF,
     MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 17:17:23 ON 10 JAN 2002

=> s l1 or l2
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'CN' IS NOT A VALID FIELD CODE
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'CN' IS NOT A VALID FIELD CODE
L3        10158 L1 OR L2

=> s botox or botulinum
L4        51132 BOTOX OR BOTULINUM

=> s l3 or l4
L5        51278 L3 OR L4

=> s anesthetic or anaesthe? or ?caine
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'ADISALERTS'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'ADISINSIGHT'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'ADISNEWS'
   6 FILES SEARCHED...
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'CEN'
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LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'IPA'
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  20 FILES SEARCHED...
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LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'NLDB'
LEFT TRUNCATION IGNORED FOR '?CAINE' FOR FILE 'PASCAL'
  30 FILES SEARCHED...
  33 FILES SEARCHED...
L6      787912 ANESTHETIC OR ANAESTHE? OR ?CAINE
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s epinephrine or phenylephrine
L7      309937 EPINEPHRINE OR PHENYLEPHRINE

=> d his

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     FILE 'HOME' ENTERED AT 17:03:52 ON 10 JAN 2002

     FILE 'REGISTRY' ENTERED AT 17:15:31 ON 10 JAN 2002
L1            1 S BOTOX/CN
L2            5 S BOTULINUM TOXIN

     FILE 'HOME' ENTERED AT 17:16:24 ON 10 JAN 2002

     FILE 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT,
     CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL,
     EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF,
     MEDLINE, NAPRALERT, NLDB, PASCAL, ...' ENTERED AT 17:17:23 ON 10 JAN 2002
L3         10158 S L1 OR L2
L4         51132 S BOTOX OR BOTULINUM
L5         51278 S L3 OR L4
L6        787912 S ANESTHETIC OR ANAESTHE? OR ?CAINE
L7        309937 S EPINEPHRINE OR PHENYLEPHRINE

=> s l5 and l6 and l7
L8           66 L5 AND L6 AND L7

=> dup rem
ENTER L# LIST OR (END):l8
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGLAUNCH,
DRUGMONOG2, KOSMET, MEDICONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L8
L9            58 DUP REM L8 (8 DUPLICATES REMOVED)

=> s composition
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  33 FILES SEARCHED...
L10    2831960 COMPOSITION

=> s mixturfe

L11          4 MIXTURFE

=> s mixture

  30 FILES SEARCHED...
L12    1652141 MIXTURE

=> s l10 or l12

  23 FILES SEARCHED...
L13    3967061 L10 OR L12

=> s l9 and l13

  24 FILES SEARCHED...
L14         45 L9 AND L13

=> d l14 1-45 ibib, kwic

L14  ANSWER 1 OF 45  USPATFULL
ACCESSION NUMBER:        2001:205895  USPATFULL
TITLE:                   Methods and compositions for the regulation of
                         vasoconstriction
INVENTOR(S):             Waeber, Christian, Boston, MA, United States
                         Moskowitz, Michael A., Belmont, MA, United States
                         Yoshimura, Shin-Ichi, Zurich, Switzerland
                         Salomone, Salvatore, Somerville, MA, United States

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2001041688      A1   20011115
APPLICATION INFO.:       US 2001-804987     A1   20010313  (9)

                                NUMBER         DATE
                         ------------------ --------
PRIORITY INFORMATION:    US 2000-188859     20000313 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    Edward R. Gates, c/o Wolf, Greenfield & Sacks, P.C.,
                         Federal Reserve Plaza, 600 Atlantic Avenue, Boston,
MA,
                         02210-2211
NUMBER OF CLAIMS:        85
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      4 Drawing Page(s)
LINE COUNT:              2803
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM   . . . a result of the increased blood flow. The second agent may be
       selected from the group consisting of analeptic, analgesic,
       anesthetic, adrenergic agent, anti-adrenergic agent, amino
       acids, antagonists, antidote, anti-anxiety agent, anti-cholinergic,
       anti-convulsant, anti-depressant, anti-emetic, anti-epileptic,
       anti-hypertensive, anti-fibrinolytic, anti-hyperlipidemia,
       anti-nauseant, anti-neoplastic. . .
DETD   . . . agents are agents having a site of action in the brain. Such
```

agents include adrenergic agent, amino acids, analeptic, analgesic, **anesthetic**, antagonists, antidote, anti-adrenergic agent, anti-anxiety agent, anti-cholinergic, anti-convulsant, anti-depressant, anti-emetic, anti-epileptic, anti-hypertensive, anti-fibrinolytic, anti-hyperlipidemia, anti-nauseant, anti-neoplastic (brain cancer), anti-obsessional agent,. . .

DETD [0125] Subjects at risk of vasospasm are currently administered a variety of preventative medications including calcium channel blockers (e.g., nimodipine), **phenylephrine**, dopamine, as well as a combination of mannitol and hyperventilation. Some forms of prophylactic treatments aim to increase the cerebral. . .

DETD [0150] A variety of other reagents also can be included in the binding **mixture**. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. which may be used to facilitate optimal. . . background interactions of the reaction components. Other reagents that improve the efficiency of the assay may also be used. The **mixture** of the foregoing assay materials is incubated under conditions under which the EDG receptor or the sphingosine-1-phosphate phosphatase normally specifically. . . perimeters of the assay may be readily determined. Such experimentation merely involves optimization of the assay parameters, not the fundamental **composition** of the assay. Incubation temperatures typically are between 4.degree. C. and 40.degree. C. Incubation times preferably are minimized to facilitate. . .

DETD . . . kinase or sphingosine-1-phosphate phosphatase polypeptides, together with pharmaceutically acceptable carriers. Antisense oligonucleotides may be administered as part of a pharmaceutical **composition**. In this latter embodiment, it is preferable that a slow intravenous administration be used. Such a pharmaceutical **composition** may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the. . .

DETD . . . was from Sigma, C. difficile toxin B was from List Biological Laboratories. 7.5 .mu.g (in 66 .mu.l water) of C. **botulinum** C.sub.3 exoenzyme (Biomol) were mixed with 25 .mu.g liposome (Transfectam, Promega), resuspended in 0.5 ml physiological solution and applied directly. . .

DETD [0177] Pentobarbital-**anaesthetized** mechanically-ventilated male rats (250-300 g, Charles River) were maintained at 37.0.+-.0.5.degree. C. A femoral vein and artery were cannulated to. . .

DETD . . . treated, in vitro, with bacterial toxins specifically affecting G.sub.i/o (B. Pertussis toxin) or Rho (C. Difficile toxin B or C. **Botulinum** C.sub.3 exoenzyme). Incubation with Pertussis toxin did not modify the S1P-induced vasoconstriction, but (as expected) decreased the response to the. . .

CLM What is claimed is:

54. The method of claim 53, wherein the second agent is selected from the group consisting of analeptic, analgesic, **anesthetic**, adrenergic agent, anti-adrenergic agent, amino acids, antagonists, antidote, anti-anxiety agent, anti-cholinergic, anti-convulsant, anti-depressant, anti-emetic, anti-epileptic, anti-hypertensive, anti-fibrinolytic, anti-hyperlipidemia, anti-migraine, anti-nauseant,. . .

L14 ANSWER 2 OF 45 USPATFULL
ACCESSION NUMBER: 2001:97606 USPATFULL

TITLE: Assay method utilizing induced luminescence
INVENTOR(S): Ullman, Edwin F., Atherton, CA, United States
Kirakossian, Hrair, San Jose, CA, United States
Pease, John S., Los Altos, CA, United States
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PRIMARY EXAMINER: Venkat, Jyothsna
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NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM U.S. Pat. No. 4,311,712 (Evans, et al.) discloses a process for preparing a freeze dried liposome **mixture**.

SUMM . . . comprising a suspendible particle having incorporated therein a chemiluminescent compound where the particle has an sbp member bound thereto. The **composition** can further comprise a suspendible particle having a photosensitizer incorporated therein.

SUMM Another embodiment of the invention concerns kits comprising in packaged combination a **composition** that includes (1) a suspendible particle having a chemiluminescent compound where the particle has an sbp member bound thereto, and (2) a photosensitizer. The kit can further include a **composition** comprising a second suspendible particle comprising a photosensitizer where the particle has an sbp member bound thereto.

DETD In one aspect of the present invention a **composition** comprising a photosensitizer and a ligand, receptor or polynucleotide binds in an assay to a **composition** comprising a chemiluminescent compound and a ligand, receptor or polynucleotide. The chemiluminescent compound can react with singlet oxygen and the. . . the photosensitizer usually by irradiation of the photosensitizer. Singlet oxygen produced by the photosensitizer that is not bound to the **composition** comprising a chemiluminescent compound is unable to reach the chemiluminescent compound before undergoing decay (t.sub.1/2 is about two microseconds in water). The **composition** comprising a photosensitizer that becomes bound to the **composition** comprising the chemiluminescent compound produces singlet oxygen that reacts with the chemiluminescent compound because such singlet oxygen can survive the. . . has a much longer lifetime, namely, greater than about one hundred microseconds. The analyte must modulate the binding between the **composition** comprising the photosensitizer and the **composition** comprising the chemiluminescent compound. Usually, at least one of the chemiluminescent compound and the photosensitizer is associated with a surface,. . .

DETD Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

DETD . . . Spore-forming Bacilli Phialophora jeanselmei

Bacillus anthracis	Microsporum gypseum
Bacillus subtilis	Trichophyton mentagrophytes
Bacillus megaterium	Keratinomyces ajelloi
Bacillus cereus	Microsporum canis
Anaerobic Spore-forming Bacilli	Trichophyton rubrum
Clostridium **botulinum**	Microsporum adouini
Clostridium tetani	Viruses
Clostridium perfringens	Adenoviruses
Clostridium novyi	Herpes Viruses
Clostridium septicum	Herpes simplex
Clostridium histoyticum	Varicella (Chicken pox)
Clostridium tertium	Herpes Zoster (Shingles)

Clostridium. . .

DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD . . . both compounds to associate with the same particle. This possibly can be further reduced by utilizing particles of only one **composition** that are associated with either the photosensitizer or chemiluminescent compound or by using two types of particles that differ in **composition** so as to favor association of the photosensitizer with one type of particle and association of the chemiluminescent compound with. . .

DETD . . . surfactant is present in from about 0.1 to 5, more usually from about 0.1 to 2 weight percent of the **mixture** and subjecting the **mixture** in an aqueous medium to agitation, such as sonication or vortexing. Illustrative lipophilic compounds include hydrocarbon oils, halocarbons including fluorocarbons,. . .

DETD . . . frequently comprised of phospholipids. Phospholipids employed in preparing particles utilizable in the present invention can be any phospholipid or phospholipid **mixture** found in natural membranes including lecithin, or synthetic glyceryl phosphate diesters of saturated or unsaturated 12-carbon or 24-carbon linear fatty. . .

DETD . . . a variety of methods, including a method described by Olsen, et

al., Biochemica et Biophysica Acta, 557(9), 1979. Briefly, a **mixture** of lipids containing the appropriate compound in an organic solvent such as chloroform is dried to a thin film on. . .

DETD . . . members, each associated with a different member of the group consisting of a photosensitizer and a chemiluminescent compound. The assay **mixture**, or a separated component thereof, is then irradiated and the light emission is measured.

DETD . . . of Reagent 1 and Reagent 2 are sufficient to provide concentrations of each antibody of about 10.sup.-6 molar. The reaction **mixture** is then incubated for a period of one hour at 25.degree. C. and then irradiated for 30 seconds with 560. . .

DETD . . . the assay Reagents 5A and 6A are combined with sample and incubated. Then, Reagent 5 and 6 are added, the **mixture** is incubated, and the remainder of the assay procedure is followed.

DETD . . . combined in one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises (1) a **composition** comprising a suspendible particle comprising a chemiluminescent compound, the particle having an sbp member bound to it, and (2) a. . .

DETD . . . added 0.64 g (0.0056 mols) diglycolic anhydride 1A1 and the reaction was left 5 hr at ambient temperature. The reaction **mixture** was concentrated and extracted with 50 mL water, 50 mL ethyl acetate. The organic phase was washed with 0.1N HCl. . .

DETD . . . mmols) of N-hydroxysuccinimide. After stirring for 16 hr., 400 mg (1.85 mmols) of mono t-Boc 1,6-diaminohexane was added, and the **mixture** was stirred for an additional 4 hours at ambient temperature. The resulting **mixture** was concentrated to a thick solution and dissolved in 1:9 methanol-ethylacetate (100 mL) and extracted with water (3.times.50 ml), 0.1N. . . with (1:1) methanol/dichloromethane, concentrated, and the residue was dissolved in

the minimum of methanol and added dropwise into water. The **mixture** was then centrifuged and the solid dried in vacuo, yielding 83% of 1A4.

DETD . . . was added 21.2 mg (0.185 mmols) methyl isocyanatoacetate and reaction was then left 24 hours at ambient temperature. The reaction **mixture** was added dropwise into a 10 ml stirring ethylacetate solution. The precipitated product was centrifuged, then resuspended in a minimum. . .

DETD The reaction **mixture** was concentrated to dryness and the product isolated using two Whatman PLC.sub.18 F plates 1000.mu., 20.times.20 cm eluant same as. . .

DETD . . . N-hydroxy succinimide were combined with 5 ml anhydrous dimethyl formamide and stirred at ambient temperature for 16 hours. The reaction **mixture** was added dropwise to a stirring solution of 13.6 mg (0.17 mmols) 21-atom long chain amine of 5-carboxyfluorescein 1A6 in. . .

DETD Using biotin-LC.sub.7 -NHS from Pierce Chemical Co., Rockford, Ill., three different levels of biotinylations (Ab.sub.IF :biotin in reaction **mixture**=1:10, 1:50, or 1:200) were performed. The Ab.sub.IF was in 0.05 M NaPi, 0.05 M NaCl/pH=7.8 at [IgG]=2.5 mg/ml. To this. . .

DETD . . . mL glass vial and warmed to 100.degree. on a laboratory hot plate. Benzyl alcohol (1.6 ml) was added and the **mixture** stirred magnetically. Stock latex suspension (2 mL, 38 nm carboxylate modified latex containing 10% solids) was added and the **mixture** allowed to equilibrate for 3 to 4 minutes. The nC.sub.10 solution (0.4 mL) was added slowly in 100 .mu.L aliquots. Heating at 100.degree. was continued for 5 minutes; then the **mixture** was allowed to cool to room temperature. After cooling, the **mixture** was applied to a column of SEPHADEX.RTM. G-25 (Pharmacia Biotech) (2.5.times.15 cm)

equilibrated with 50% aqueous ethanol. The latex containing. . .

DETD . . . mL Erlenmeyer flask and warmed to 110.degree. on a laboratory hot plate. Benzyl alcohol (8 mL) was added and the **mixture** stirred magnetically. The nC.sub.10 solution (2 mL) was added followed immediatley by stock latex suspension (10 mL, 175 nm carboxylate. . . minutes while stirring vigorously. The flask was then placed in a room temperature water bath to cool. After cooling, the **mixture** was diluted with an equal volume of ethanol and immediately centrifuged at 15,000 rpm (Sorval, SA 600 rotor) for two. . .

DETD . . . 125 mL Erlenmeyer flask and warmed to 100.degree. on a laboratory hot plate. Benzonitrile (9 mL) was added and the **mixture** stirred magnetically. The BA-C.sub.18 solution (1 mL) was added followed immediately by stock latex suspension (10 mL, 175 nm latex. . . minutes while stirring vigorously. The flask was then placed in a room temperature water bath to cool. After cooling, the **mixture** was diluted with an equal volume of 50% aqueous ethanol and immediately centrifuged at 15,000 rpm (Sorval, SA 600 rotor). . .

DETD . . . and a small aliquot used for the reaction) together and incubating for three hours at 4.degree. C. In the reaction **mixture**, the molar ratio of the reactants was antibody:Biotin-LC.sub.7 -NHS=1:25. The uncoupled biotin was removed by SEPHADEX.RTM. G-25 (Pharmacia Biotech) column.. . .

DETD . . . of 100 mg/mL 6-carboxyfluorescein and 30.6 mg/mL of NHS in DMF,

0.4 mL of 275 mg/mL DCC was added. The **mixture** was stirred overnight at room temperature in the dark. The formed dicyclohexylurea was removed by filtration. The formation of F-NHS. . .

DETD . . . incubation at room temperature overnight with stirring in the dark. The molar ratio of F-NHS:LC.sub.9 was 1:40. Then, the reaction **mixture** was diluted 1/20 with 0.5 M NaPi/pH 5.0, the pH of the **mixture** was adjusted to 5.0 by addition of phosphoric acid (1.0 M) and the whole **mixture** was loaded onto a (2.5.times.10 cm) of BioRex-70.RTM. column, equilibrated in 0.5 M NaPi/pH=5.0. After loading, the column was washed. . .

DETD The following day, the reaction **mixture** was diluted with water and extracted from the reaction solution with methylene chloride. The methylene chloride extracts were dried over. . .

DETD The liposomes were prepared by methanol dilution method. Typically a **mixture** of lipids: Cholesterol (2.0 mg), DPPC (Avanti Polar Lipids, Alabaster, Ala.) (23.8), DPPG (Avanti Polar Lipids, Alabaster, Ala.) (6.5 mg),. . . liposomes were slowly added into stirred succinylated avidin-SH (prepared as described below) solution in buffer-B. After flushing with argon this **mixture** was mixed gently (no stirring bar) overnight at 4.degree. C. The excess maleimide groups were blocked with 2 mM mercaptosuccinic. . . acid to a final 5

mM concentration to block the excess thiol groups (30 min at 4.degree. C.). The reaction **mixture** was then concentrated to 2.5-3 ml by means of a CENTRIPREP-30.RTM. (W. R. Grace & Company) device and the uncoupled. . .

DETD . . . less than 1% of the reaction volume), and the solution was incubated for 2 hours. The pH of the reaction **mixture** was kept at 7.4 by addition of 0.5M Na.sub.2 HPO.sub.4. The protected thiol groups (thioester) were liberated with hydroxylamine (0.1M,. . .

DETD . . . protein solution (15 m of 0.02M Borax, 0.08 M NaCl, 2 mg/ml 3Gl

IgG (Ab.sub.F), 8 mg/ml BSA/pH 8.9). The **mixture** was gently shaken (no stirring) overnight at 4.degree. C. The remaining reactive groups on the beads, if any, were blocked. . .

DETD . . . M NaPi/pH 5.8 and transferred into a stirred avidin solution

(15 ml of 0.025 M Borax, 1.33 mg/ml avidin/pH9.1). The **mixture** then was mixed gently at 4.degree. C. overnight. The avidin on the beads was succinylated by adding 20 .mu.l of. . . at 4.degree. C. for 1 hour. The beads were blocked with 7 mg/ml BSA (the final concentration in the reaction **mixture**) for 60 min. at 4.degree. C. Finally the beads were washed three times with 0.05 M NaPi, 0.15 M NaCl/pH7.6. . .

DETD . . . (25 ml). N-hydroxysuccinimide (3.22g, 28 mmole) was added as a solid to the DMF solution and allowed to dissolve. The **mixture** was then cooled in an ice bath. Dicyclohexyl carbodiimide (5.8 g, 28 mmole) was dissolved in dry DMF (10 ml) and added all at once to the cold DMF solution. The **mixture** was stirred at ice bath temperature for 30 min. and then allowed to come to room temperature. The course of. . .

DETD 4,9-Dioxa-1,12-dodecane diamine (25.5 g, 125 mmole) was diluted with dry DMF (10 ml). The fluorescein NHS ester reaction **mixture** was cooled in ice under an argon atmosphere and the diamine solution added dropwise over a period of 5 minutes.. . . The course of the reaction was followed by tIc using the above system. When the reaction was judged complete, the **mixture** was diluted with water (100 ml) and cooled in ice to precipitate dicyclohexylurea which was removed by filtration.

DETD . . . top of a silica gel column (2.5.times.25 cm) equilibrated with dichloromethane. The column was eluted with the above tlc solvent **mixture**. Fractions containing product were pooled and solvent removed on the rotovap. The residue was taken up in ethanol and filtered.. . .

DETD . . . beads/ml) and 100 .mu.L of biotin-LC.sub.21 -F (varying amounts) in 0.05 NaPi, 0.15 M NaCl, 4 mg/ml BSA/pH 7.6. This **mixture** was incubated at room temperature for 1.5 hours with shaking in the dark. Finally, each tube was illuminated with halogen. .

DETD . . . M NaPi, 0.15 M NaCl, 4 mg/ml BSA/pH 7.6) and 50 .mu.l Ab.sub.1 (.alpha.HCG)-OD/BA-C.sub.18 reagent containing 5.times.10.sup.8 oil droplets. This **mixture** was incubated for one hour at room temperature in the dark. Then, 50 .mu.l of 2 .mu.g/ml Strepavidin-T680 in assay. . .

CLM What is claimed:

1. A **composition** comprising: a) first suspendible particles comprising a chemiluminescent compound capable of reacting with singlet oxygen, and b) second suspendible particles. . .

2. The **composition** of claim 1, wherein said first suspendible particles have bound thereto a specific binding pair member.

3. The **composition** of claim 2, wherein said first suspendible particles are selected from the group consisting of latex particles, lipid bilayers, oil. . .

4. The **composition** of claim 2, wherein said chemiluminescent compound contains an olefin group.

5. The **composition** of claim 2, wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .

6. The **composition** of claim 2, wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-alkyl acridans, enolethers, enamines, and 9-alkylidene. . .

7. The **composition** of claim 2, wherein said specific binding pair member is selected from the group consisting of receptors, ligands, and polynucleotides.

. . .

8. The **composition** of claim 1, wherein said second suspendible particles are selected from the group consisting of latex, lipid bilayers, oil droplets,. . .

9. The **composition** of claim 1, wherein said second suspendible particles have bound thereto a specific binding pair member.

10. The **composition** of claim 9, wherein said specific binding pair member is selected from the group consisting of receptors, ligands, and polynucleotides.

. . .

11. A **composition** comprising: a) first suspendible particles comprising a chemiluminescent compound that is capable of reacting with singlet oxygen, wherein said first. . .

12. The **composition** of claim 11, wherein said chemiluminescent compound contains an olefin group.

13. The **composition** of claim 11, wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .

14. The **composition** of claim 11, wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-alkyl acridans, enolethers, enamines, and 9-alkylidene. . .

15. The **composition** of claim 11, wherein said first specific binding pair member is selected from the group consisting of receptors, ligands, and. . .

16. The **composition** of claim 11, wherein said second specific binding pair member is selected from the group consisting of receptors, ligands, and. . .

17. The **composition** of claim 11, wherein said first suspendible particles, said second suspendible particles, or both, are latex particles.

18. A kit comprising: (a) a first **composition** comprising a member of a specific binding pair (sbp) member associated, via at least one covalent or non-covalent bond, with. . . in its excited state of activating oxygen to its singlet state, and ii) a suspendible particle; and (b) a second **composition** comprising an sbp member associated, via at least one covalent or non-covalent bond, with i) a chemiluminescent compound, capable of. . .

19. The kit of claim 18, wherein the suspendible particle in said first **composition**, said second **composition**, or both, is a latex particle.

20. The kit of claim 18, wherein said second **composition** further comprises a fluorescent energy acceptor.

23. A kit comprising: (a) a first **composition** comprising an antibody as a member of a specific binding pair (sbp) associated, via at least one covalent or non-covalent. . . its excited state of activating oxygen to a singlet state, and ii) a suspendible latex particle; and (b) a second **composition** comprising an antibody as a sbp member associated, via at least one covalent or non-covalent bond, with i) an enol. . .

25. The kit of claim 23, wherein said second **composition** further comprises a fluorescent energy acceptor.

27. A kit comprising, in packaged combination, a) a **composition** comprising a first suspendible particle, wherein said first suspendible particle comprises a chemiluminescent compound capable of emitting light upon interaction. . . oxygen, and wherein said first suspendible particle is bound to a first specific binding pair (sbp) member, and b) a **composition** comprising a second suspendible particle, wherein said second suspendible particle comprises a photosensitizer capable, in its excited state, of activating. . .

L14 ANSWER 3 OF 45 USPATFULL

ACCESSION NUMBER:	2000:174129 USPATFULL
TITLE:	Preparation for the application of agents in mini-droplets
INVENTOR(S):	Cevc, Gregor, Heimstetten, Germany, Federal Republic of
PATENT ASSIGNEE(S):	Idea AG, Munich, Germany, Federal Republic of (non-U.S. corporation)

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APPLICATION INFO.:	US 1992-844664		19920408	(7)

	NUMBER	DATE
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LEGAL REPRESENTATIVE:	Davidson, Davidson & Kappel, LLC
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NUMBER OF DRAWINGS:	31 Drawing Figure(s); 21 Drawing Page(s)
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . the work by Price (1981, op.cit.). To date it has been common to simply add chemical penetration enhancers to the **mixture** of agent and other molecules; applications to human skin were the only case in which additives were sometimes applied in. . .

SUMM . . . acids) and of lipid vesicles, Gesztes und Mezei (1988, Anesth. Analg. 67, 1079-1081) have succeeded in inducing local analgesia with **lidocaine**-containing carriers; however, the overall effectiveness of the drug in this preparation was relatively low and its effects were only observed. . .

DETD . . . optimized for applications on skin (cf. patent application P 40 26 834.9-41) was based on the use of a carrier **composition** with an optimal lipid/surfactant ratio in the range of L/S=1-40/1. However, a transfersome must mainly have an optimal elasticity, which. . .

DETD . . . medical agents. Transfersomes can carry water- or fat-soluble agents to various depths at the application site, depending on the transfersomal **composition**, application dose, and form. Special properties which cause a carrier to behave as a transfersome can be realized for phospholipid. . .

DETD Carriers according to this invention can consist of one or several components. Most commonly, a **mixture** of basic substances, one or several edge-active substances and agents is used. Lipids and other amphiphiles are best suited basic. . .

DETD at least one agent which can induce systemic anesthesia or analgesia, e.g. chlorobutanol, ketamine, **oxetacaine**, propanidide and thiamylal, aminophenol-derivatives, aminophenazol-derivatives, antranilic acid- and arylpropione acid derivatives, azapropazone, bumadizone, chloroquin- and codeine-derivatives, diclophenac, fentanil, ibuprofen, indometacine,. . . acid, meptazonol, methadone, mofebutazone, nalbufine, Na-salt of noramidopyrinium-methanesulfonate, nefopam, normethadone, oxycodone, paracetamol, pentazocine, pethidine, phenacetine, phenazocine, phenoperidine, pholcodine, piperylone, piritramide, **procaine**, propyphenazone, salicylamide, thebacone, tiemonium-odide, tramadone;

DETD . . . such as most of the cardiacs and beta-blockers, ajmaline, bupranolol, chinidine, digoxine derivatives, diltiazem, disopyramidedihydrogensulfate, erythromycine, disopyramide, gallopamil, ipratropiumbromide, lanatoside, **lidocaine**, lorcainide, orciprenalinesulfate, **procaine** amide, propafenone, sparteinesulfate, verapamil, toliprolol.

DETD at least one substance with a neurotherapeutic activity, such as **anaesthetics** and vitamins, atropine-derivatives, benfotiamine, choline-derivatives, caffeine, cyanocobolamine, alpha-liponic acid, **mepivacaine**, phenobarbital, scopolamine, thiaminchloride hydrochloride, etc., and, most notably, **procaine**;

DETD at least one opthalmic, in many cases from the groups of **anaesthetics**, antibiotics, corticoids, eye-tonics, chemotherapeutics, glaucome agents, virustatics, antiallergics, vasodilatators, or vitamins;

DETD at least one sympathicomimetic, e.g. bamethane, buphenine, cyclopentamine, dopamine, L-(-)-ephedrine, **epinephrine**, etilefrine, heptaminol, isoetarine, metaraminol, methamphetamine, methoxamine, norfenefrine, phenylpropanolamine, pholedrine, propylhexedrine, protokylol or synephrine;

DETD at least one substance with a vasoconstricting action; often, adrenalone, **epinephrine**, felypressine, methoxamine, naphazoline, oxymetazoline, tetryzoline, tramazoline or xylometazoline are used for this purpose;

DETD . . . aflatoxin B2-alpha, aflatoxin G1, aflatoxin G2, aflatoxin G2-alpha, aflatoxin M1, aflatoxin M2, aflatoxin P1, aflatoxin Q1, alternariol-monomethyl ether, aurovertin B, **botulinum** toxin D, cholera toxin, citreoviridin, citrinin, cyclopiazonic acid, cytochalasin A, cytochalasin B, cytochalasin C, cyrochalasin D, cytochalasin, cytochalasin H, cytochalasin. . .

DETD . . . example, acetylcholine, adrenaline, adrenocorticotropic hormone, angiotensine, antidiuretic hormone, cholecystokinine, chorionic gonadotropine, corticotropine A, danazol, diethylstilbestrol, diethylstilbestrol glucuronide, 13,14-dihydro-15-keto-prostaglandins, 1-(3',4'-dihydroxyphenyl)-2-aminoethanol, 5,6-dihydroxytryptamine, **epinephrine**, follicle stimulating hormone, gastrin, gonadotropin, .beta.-hypophamine, insulin, juvenile hormone, 6-ketoprostaglandins, 15-ketoprostaglandins, LTH, luteinizing hormone

releasing hormone, luteotropic hormone, .alpha.-melanocyte stimulating. . .

DETD . . . substances, surfactants, lipids, agents or additives with one or several chiral carbon atoms can be used either as a racemic **mixture** or in the form of optically pure enantiomers.

DETD . . . to be a complex function of the carrier size, often showing a maximum depending on the chosen carrier and/or agent **composition** .

DETD . . . active substances with a tendency to leave carriers and move into a barrier give rise to a locally variable carrier **composition**, etc. These interdependencies should be thought of and considered prior to each individual application. In the search for a set. . .

DETD Next, the carrier **composition** or concentration is adapted by reducing the edge activity in the system to an extent which ensures the vesicle stability. . . the one hand, a mechanical tendency of the carrier components to "stay together"; on the other hand, that the carrier **composition** during the transport, and in particular during the permeation process, does not change at all or not much. The position. . .

DETD . . . body systems through a system of blood and lymph vessels, the precise drug fate being dependent on the carrier size, **composition** and formulation.

DETD . . . cm of skin surface, the given masses pertaining to the basic carrier substance. The optimal mass depends on the carrier **composition**, desired penetration depth and duration of action, as well as on the detailed application site. Application doses useful in agrotechnics. . .

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD First Tween 80 and subsequently phosphate buffer are added to appropriate quantities of PC. The resulting **mixture** is agitated at room temperature for 4 days. The further procedure is as described in examples 40-49.

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD The optical density (OD (400 nm)) of a lipid-triton **mixture** after a 10-fold dilution provides insight into the vesicle solubilization; this is represented in the right panel of FIG. 8.. . .

DETD **Composition**:

DETD **Composition**:

DETD . . . concentration series with increasing L/S values between 1/4 and 2/1 (and a final total lipid concentration of 2.5%). Each lipid **mixture** in a glass vial was then supplemented with 4.5 ml of buffer. Subsequently, the resulting suspension was mixed in an. . .

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:

DETD **Composition**:
DETD **Composition**:
DETD **Composition**:
DETD . . . each case, 35 mg of lipid are mixed with tritium-labelled dipalmitoylphosphatidylcholine in chloroform. After thorough drying under vacuum, the resulting **mixture** is suspended in 0.32 ml of buffer; the nominal surfactant/lipid ratios are 0; 0.125; 0.167; 0.263; 0.5 and 1 mol/mol.. . .
DETD On the back of an immobilized nude-mouse **anaesthesized** with ether six areas of 1.times.1 cm are marked. Each of these areas is covered with 20 microliters of a. . .
DETD . . . normalized values are also given which were taken from our patent application pertaining to the use of liposomes for topical **anaesthesia**. Optimal transfersomes are appreciably better than non-optimal preparations containing surfactants.
DETD **Composition**:
DETD . . . case 35 mg of lipid (PC and deoxycholate) are mixed with tritium-labelled dipalmitoylphosphatidylcholine in a chloroform solution. The resulting lipid **mixture** is dried and then dissolved in 30 microliters of warm, absolute ethanol. This solution is then mixed with 0.32 ml. . .
DETD Tails of 2 **anaesthesized** mice are treated with 50 microliters of a corresponding vesicle suspension for 15 minutes. Two control animals obtain an i.v.. . .
DETD **Composition**:
DETD On the abdomen of NMRI-mice in general **anaesthesia**, which three days before were depillated using medical tweezers, 10 microliters of a vesicle suspension containing inulin in every case. . .
DETD **Composition**:
DETD Samples are prepared essentially as described in examples 62-75. A **mixture** of aqueous salt solution and human recombinant insulin (with 6.75 mg m-cresole) is mixed with a lipid solution in ethanol.. . .
DETD **Composition**:
DETD **Composition**:
DETD . . . suspensions independent of the precise L/S ratio; 10 weight-% of agent cannot be incorporated into stable transfersomes of the given **composition**.
DETD **Composition**:
DETD **Composition**:
DETD **Composition**:
DETD **Composition**:
DETD **Composition**:
DETD This preparation is produced as described in example 166, with only minor modifications. The main difference is that the lipid/insulin **mixture** is hand-filtered through a 0.22 .mu.m polycarbonate filter (Sartorius) using a 1 ml injection already few minutes after **mixture** preparation. The final volume of the suspension is 1.2 ml; the nominal lipid/cholate ratio is 2.8/1, in lipid membranes approx.. . .
DETD **Composition**:
DETD **Composition**:
DETD **Composition**:
DETD **Composition**:
CLM What is claimed is:
. . . is selected from the group consisting of an adrenocorticosteroid or its analogues, an androgen, an antiandrogen, an anabolic steroid, an **anaesthetic**, an analgesic, an antiallergic, an antiarrhythmic, an antiarterosclerotic, an antiasthmatic, an antidepressant, an

antipsychotic, an antidiabetic, an antidote, an antiemetic,. . .

L14 ANSWER 4 OF 45 USPATFULL

ACCESSION NUMBER:	2000:121520 USPATFULL
TITLE:	Method for treating painful conditions of the anal region and compositions therefor
INVENTOR(S):	Fogel, Barry S., Waban, MA, United States
PATENT ASSIGNEE(S):	Synchroneuron, LLC, Waban, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6117877		20000912
APPLICATION INFO.:	US 1999-258828		19990225 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-31858, filed on 27 Feb 1998		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Cook, Rebecca		
LEGAL REPRESENTATIVE:	Choate, Hall & Stewart		
NUMBER OF CLAIMS:	22		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1104		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Method and **composition** for treating painful conditions of the anorectal region. The compositions include a combination of an .alpha.-adrenergic blocker and sucralfate, a combination of .alpha.-adrenergic blocker and **lidocaine**, and a combination of an .alpha.-adrenergic blocker, **lidocaine**, and sucralfate. Alternatively, the **composition** may contain only an .alpha.-adrenergic blocker. Additional active ingredients for reduction of anal pain may be added to the **composition**, particularly capsaicin. The compositions may be included in a petrolatum base along with a water soluble lubricant. These compositions have. . .

SUMM . . . determined by the intensity of the contraction of the IAS. These treatments include lateral sphincterotomy, injection of the sphincter with **botulinum** toxin (Maria et al., Ann Surg, 1998 November, 228(5):664-9), and application of nitroglycerin ointment (Manookian et al.; Ann Surg 1998. . . of treatment for chronic anal fissures recommends beginning with nitroglycerin ointment. If the fissure has not healed in six weeks, **botulinum** toxin injections are given. That review notes that "considerable educational effort is required to successfully adjust the dose" of nitroglycerin.

.

SUMM . . . minutes. A separate approach, described by Parischa and Kallo in U.S. Pat. No. 5,437,291, makes use of direct injections of **botulinum** toxin into the affected area for treatment of gastrointestinal muscle disorders and other smooth muscle dysfunction. They report that the benefits of **botulinum** toxin injection appear to be sustained for several months.

SUMM **Lidocaine**, a topical **anesthetic**, has been used as a treatment for another painful rectal condition, ulcerative proctitis (Bjorck et al., Scandinavian Journal of Gastroenterology,. . .

SUMM In co-pending, commonly-owned U.S. patent application Ser. No. 09/031,858, incorporated by reference herein, I show that sucralfate, together with nitroglycerin, **lidocaine**, or both, is efficacious for the treatment of anal fissures, and inferred its utility

for other painful conditions of the. . .

SUMM One aspect of the invention is a **composition** comprising an .alpha.-adrenergic blocker alone at an effective and tolerable dose. Another aspect of the present invention is a **composition** comprising the combination of an .alpha.-adrenergic blocker together with sucralfate. Yet another aspect is a **composition** comprising a combination of an .alpha.-adrenergic blocker together with a local **anesthetic** (preferably **lidocaine**). In addition, the inventive **composition** may combine .alpha.-adrenergic blocker, together with sucralfate and a local **anesthetic** to achieve a synergistic effect. These compositions have analgesic properties and are useful for treatment of anal fissures and other. . .

SUMM . . . analgesic effect. One particularly preferred active ingredient is capsaicin. According to the present invention, capsaicin may be added to any **composition** for treatment of anal pain. Continued capsaicin treatment, may be effective in reducing some of the reflex contractions of the. . . uncomfortable sense of fecal urgency in an individual with a painful anal condition. Capsaicin can be co-administered with a local **anesthetic** agent to diminish the burning sensation that accompanies its initial application to skin or mucosa. In other preferred embodiments, any. . .

SUMM . . . symptoms, with tolerable adverse effects. A person skilled in the art will recognize that the optimal dose of a pharmaceutical **composition** administered will vary from one individual to another. When considering a topical preparation for anorectal use, dosage in individual patients--regarding. . .

SUMM "Non-toxic": As used herein, "non-toxic" refers to the administration of a dose of the **composition** for treatment of anal pain, wherein the active components in the **composition** cause no adverse effects intolerable to the patient onto which the **composition** is administered.

SUMM "Active agent": "Active agent", as used herein, refers to any component in a **composition** of the present invention that increases the analgesic effects of that **composition** and can be added to the compositions of the present invention to enhance their ability to reduce the symptoms associated with anorectal disease. In the **composition** of the present invention, .alpha.-blockers, **lidocaine** and sucralfate are all active agents. "Active agent" is also used to refer to any component in any known **composition** (e.g. preparation H) that increase the analgesic effects of that **composition**.

SUMM . . . differs from the use of "active agent", as used herein, to mean any component that can be added to a **composition** that has some biological effect, whether the biological effect is directly related to anorectal disease or not. The biological effect is preferably curative. Such components might have analgesic or **anesthetic** effects, for example, capsaicin, corticosteroids (hydrocortisone and triamcinolone), non-steroidal antiinflammatory drugs (including specifically diclofenac opiates), or salicylates (salsalate, sulfasalazine). Such. . .

SUMM . . . is used generally to refer to anything with relevant biological activity that is added to biologically inert ingredients in a **composition** intended for therapeutic use.

DETD . . . and antagonists, the IAS responds like the internal urethral

sphincter, with which it shares a common developmental origin. As expected, **phenylephrine**, an .alpha.1 agonist, increases tone in the IAS. However, it is unexpected that a tolerable dose of an .alpha.-adrenergic blocker. . .

DETD . . . Case Report 3). Within 5 minutes, she had substantial relief-->50%. She compared the cream with a combination cream containing nitroglycerin, **lidocaine** and sucralfate; results were similar. The patient had a headache after applying the cream with nitroglycerin, but did not experience. . .

DETD As noted above, in co-pending patent application Ser. No. 09/031,858, I reported that a cream containing nitroglycerin, **lidocaine**, and sucralfate was efficacious for the treatment of the pain of anal fissures, and that it was more efficacious than nitroglycerin alone, or nitroglycerin with **lidocaine**, **lidocaine** and sucralfate alone, or nitroglycerin and sucralfate alone.

DETD Three factors contribute to the synergistic efficacy of the combination: 1) the local **anesthetic** effect of **lidocaine** is based on a different mechanism of action than the analgesic effect of nitroglycerin; 2) sucralfate serves to keep the. . . the efficacy of an .alpha.1-adrenergic blocker alone for anal pain, I inferred that the combination of an .alpha.1-adrenergic blocker with **lidocaine** and sucralfate, or with **lidocaine** or sucralfate alone, would provide relief from anal pain. Such combination would circumvent the use of nitroglycerin, which, as noted. . . above, causes adverse side effects, especially headaches, in some patients. In addition, the combined use of an .alpha.-adrenergic blocker with **lidocaine** and sucralfate provides therapeutic efficacy at a lower than toxic dose of the .alpha.-adrenergic blocker due to the synergistic activity. . .

DETD In one preferred embodiment, the .alpha.1-adrenergic blocker is used alone. Alternatively the .alpha.1-adrenergic blocker is combined with a local **anesthetic** for treatment of painful anal conditions. One skilled in the art will recognize any local **anesthetic**, such as, without limitation, **lidocaine**, **benzocaine**, **dibucaine bupivacaine**, **tetracaine** etc., is acceptable for use in the present invention. Preferred local anesthetics include **lidocaine**, **benzocaine**, **dibucaine**, and **bupivacaine**. A most preferred local **anesthetic** is **lidocaine**.

DETD . . . pharmacodynamic properties. In yet another preferred embodiment of the present invention, the .alpha.-adrenergic blocker is combined with both a local **anesthetic** and sucralfate or similar anti-inflammatory, as mentioned above, for application to the anal region.

DETD It is preferable that any **composition** described herein is administered at effective and non-toxic dosages, such that the patient experiences relief from symptoms in the absence. . . terazosin or doxazosin would be administered in the dose range of 0.1-1.0 mg per 5 ml of formula. A local **anesthetic** of the same potency as **lidocaine** would be administered at a concentration in the dose range of 20-200 mg per 5 ml of formula. Sucralfate is typically administered at 50-500 mg per 5 ml of formula. A particularly preferred **composition** of the present invention is a **composition** in which each standard 5 ml dose contains 0.1-1.0 mg of doxazosin or

terazosin, 20-200 mg of **lidocaine**, and 50-500 mg of sucralfate. Specific concentrations may be adjusted according to patient tolerance. Dosage in individual patients--regarding the concentration. . .

DETD . . . present invention provides compositions containing .alpha.-adrenergic blockers and additional active ingredients. One particularly attractive active ingredient of the present inventive **composition** is capsaicin.

DETD . . . U.S. Pat. No. 5,788,982 by Nadoolman, et al., and U.S. Pat. No. 4,997,853 by Bernstein describes co-administration of capsaicin and **lidocaine** generally to the skin, to reduce the burning associated with the application of capsaicin alone. U.S. Pat. No. 5,854,291 by Laughlin et al., describes use of capsaicin in conjunction with a topical **anesthetic** for treatment of hemorrhoidal pain and itching. Capsaicin is a desirable active ingredient for treatment of anal pain, not only. . . an individual with a painful anal condition. Thus, I proposed that the active ingredient capsaicin may be added to any **composition** for treatment of anal pain.

DETD . . . membranes (see Case Report 6), especially mucous membranes of the anal region. More preferably, capsaicin is combined with a local **anesthetic** at such dose that the capsaicin is effective at reducing pain in the anal region, yet is tolerable upon application.. . . of Substance P from the local. In a particularly preferred embodiment, capsaicin (at a tolerable dose or with a local **anesthetic**) is combined with an .alpha.1-adrenergic antagonist for treatment of anal pain.

DETD . . . combination of .alpha.-adrenergic blocker with an additional active ingredient can be enhanced further by the addition of either a local **anesthetic**, sucralfate or both. Such compositions may be applied to the anal region at effective and non-toxic dosages for treatment of. . .

DETD . . . preferably any two of a steroidal antiinflammatory (e.g., a corticosteroid), a non-steroidal antiinflammatory drug (including specifically diclofenac opiates), a local **anesthetic**, sucralfate or a similar disaccharide, capsaicin (with a local **anesthetic**, i.e., **lidocaine**) or capsaicin (in a tolerable dosage or preparation). Such combinations would provide improved relief over treatment with the .alpha.-antagonist alone.

DETD . . . treatment of anorectal conditions, including without limitation Anusol, Tronolane, Preparation H, and generic equivalents of those products. Other examples are A-**Caine**, Americane, Anusol, Balneol, BiCozene, Blue-Gray, Calmol 4, Cortef Rectal Itch Ointment, Diothane, **Epinephiricaine** Ointment, Gentzy Wipes, Hemorrin, HTO Ointment, HTO Stainless, Lancane, Mediconet, Non-Steroid Protofoam, Nupercainal Ointment, Nupercainal Suppositories, Pazo, Perifoam, Peterson's Ointment, **Pontocaine**, Preparation H Cleansing Pads, Proctodon, Rantex, Rectal Medicone Suppositories, Rectal Medicone Unquent, **Tanicaine** Ointment, **Tanicaine** Suppositories, Tucks Cream and Ointment, Tucks Pads, Wyanoid Ointment and Wyanoid Suppositories. See also Federal Register, 45 33576, May 22,. . .

DETD . . . or reducing IAS pressure, including without limitation nitroglycerin, other nitrates (e.g. isosorbide dinitrate), other nitric

oxide donors, and L-arginine. Any **composition** containing any one of these ingredients could be reformulated to contain an .alpha.-adrenergic blocker, (i.e., an .alpha.1-adrenergic antagonist or a non-specific .alpha.-adrenergic antagonists with sufficient .alpha.1-adrenergic antagonist effects.). Alternatively, capsaicin, with or without a local **anesthetic** such as **lidocaine**, can be used to replace the active agents or ingredients in the above-mentioned marketed over-the-counter compositions.

DETD . . . temporarily relieve pain, burning, itching, discomfort and irritation by preventing transmission of nerve impulses. Non-limiting examples of topical anesthetics include **benzocaine**, pramoxine hydrochloride, benzyl alcohol, **dibucaine** hydrochloride, dicylonine hydrochloride, **lidocaine**, **tetracaine** and **tetracaine** hydrochloride. See also Federal Register, 45 35576, May 27, 1980. In general, the local or topical **anesthetic** may be present in any amount which is effective in the practice of the treatment of anal disease.

DETD . . . reduce inflammation, irritation and swelling by constricting the symptomatic abnormally large conglomerates of blood vessels. Non-limiting examples include ephedrine and **epinephrine**. See also Federal Register, 45 35576, May 27, 1980.

DETD . . . capsaicin and other pharmacologic compounds used in the treatment of the symptoms of anorectal disease are formulated in the same **composition**, for example with a wound healing compound, a protectant, a vasoconstrictor, or a local **anesthetic** or with more than one of these compounds.

DETD Compositions in the form of ointments, creams, gels, pastes, suppositories, pads, liquids, emulsions, foams, aerosols, semisolid powders, or any other **composition** suitable for topical administration are acceptable compositions for the topical treatment of the anorectal pain. In another aspect, the **composition** of the invention may contain conventional materials and ingredients and conform to pharmacologically accepted formulations. Some of the compositions listed. . . inflamed tissues and sphincter muscle fibers, and providing more accurate and controllable dosing. Accidental spilling and undesired contact with the **composition** can also be minimized with such types of formulations.

DETD . . . glycols and similar agents, as they are readily compatible with water or other diluents which may be formulated in the **composition**. Alternatively, an emulsion base may be employed to impart the desired thickening effect, as well as the emollient effect of. . .

DETD . . . like of different viscosities depending upon the desired consistency and concentration of active compound(s) which may be incorporated into the **composition**. Other thickening agents which may be suitable for employment herein include but are not limited to water-dispersible gums, carboxyvinyl polymers,. . .

DETD . . . dosage forms. Squeeze tubes for lotions and ointments and cofton stick applicators may be employed for topical application of the **composition** for liquids ranging from those of water-like viscosity of the more viscous formulations of thickened compositions and for powders and. . .

DETD In treatments according to the invention, an amount of the **composition** of the invention is contacted with or applied to the affected anal area or proximate thereto such that an effective amount of

.alpha.-adrenergic antagonist or other active compound is administered. The amount of active compound(s) or **composition** which is employed should be effective for the amelioration, control and/or healing of the anal disease and for the prompt and dramatic control or relief of pain resulting from or associated with the disease. For example, an ointment **composition** of the invention can be applied topically at each application to the external anus and to the distal anal canal. . .

DETD . . . Series 2: 4 subsequent patients, all but one with anoscopically confirmed anal fissures, were treated with the combination of nitroglycerin, **lidocaine**, and sucralfate, with the expectation of even better relief. (Patient #4 suffered from chronic anal pain of unknown cause.) All. . .

DETD . . . required any oral analgesics, sitz baths, or other treatments to relieve pain, as soon as they had access to the nitroglycerin-**lidocaine**-sucralfate cream.

DETD . . . treated. He had six weeks of pain prior to the treatment. We treated him on alternate days with either the **composition** including nitroglycerin, **lidocaine** and sucralfate or the **composition** without the sucralfate. He was instructed to reapply the formula any time the pain began to recur. The three ingredient. . .

DETD . . . anal fissure can be lower than that reported in the literature.

These cases also show that adding nitroglycerin to the sucralfate-**lidocaine** combination improves efficacy. The three additional cases are shown in the table below:

DETD Patient #5 in the table above received the nitroglycerin-**lidocaine**-sucralfate formula discussed above (formula A) and a formulation without sucralfate (formula B) in the sequence A-B-A over three days. The. . .

DETD Patient #6 received a modified formula with 30 grams of 2% nitroglycerin ointment per 500 grams of the nitroglycerin-**lidocaine** -sucralfate **mixture**. The concentration of nitroglycerin in this **mixture** (0.12%) was lower than the 0.2% concentration reported in recent randomized controlled trials of the use of nitroglycerin as a single compound. Nonetheless, the **mixture** was efficacious and did not cause headaches (or any other side effects).

This case supports the inventor's premise that nitroglycerin in combination with sucralfate and **lidocaine** is superior to nitroglycerin alone. The combination is efficacious at lower doses of nitroglycerin and the combination is less likely. . .

DETD . . . 25% of the pain remained after application. This case supports the relevance of nitroglycerin to the analgesic activity of the **mixture**, even in conditions other than anal fissure, where the efficacy of nitroglycerin is well established.

DETD . . . that contains nitroglycerin will be more efficacious if it also contains sucralfate. A cream or ointment containing nitroglycerin, sucralfate, and **lidocaine** is especially efficacious.

DETD . . . Within 5 minutes, the patient has substantial relief (>50%). The patient compared the .alpha.-adrenergic cream with a cream containing nitroglycerin, **lidocaine** and sucralfate and reported that relief was similar. The patient chose to continue using the doxazosin cream.

DETD 10 grams **lidocaine** base

DETD Conclusions: Case Reports 4 and 5 establish that a combination of

lidocaine, sucralfate and an .alpha.1-adrenergic antagonist is efficacious and tolerable treatment for anal fissures. Together with Case Report 3, showing that. . . .alpha.1-adrenergic antagonist alone is efficacious, it can be inferred that the combination of an .alpha.1-adrenergic antagonist with either sucralfate or **lidocaine** (rather than both) will be efficacious.

DETD Tolerability of Capsaicin in a Formula Containing a Local **Anesthetic**

DETD . . . potential usefulness of capsaicin in the anal region, I did an experiment on the tolerability of capsaicin alone and with **lidocaine**, and with **lidocaine** and dozasosin. A small amount of 0.075% capsaicin cream amount (about 5 mm of Zostrix.RTM. cream, as it comes from. . . with copious amounts of water. The same amount of capsaicin cream was then combined with an equal amount of 5% **lidocaine-prilocaine** cream (EMLA.RTM. Cream), The burning sensation was present, but was tolerable. Finally, the same amount of capsaicin cream was combined with the above described doxazosin-**lidocaine**-sucralfate cream. The burning sensation was less than with the EMLA Cream, and was easily tolerated.

DETD . . . Administration of 0.075% capsaicin cream alone to the anal region is intolerable, but if it is combined with a local **anesthetic** ingredient that reduces the initial burning sensation, it becomes tolerable. Once it is made tolerable by the concurrent presence of a local **anesthetic**, capsaicin, with its known local analgesic properties, becomes a safe and effective active ingredient in a **composition** for the relief of anal pain. It would be expected to augment the effects of ingredients that work by different. . .

DETD . . . single agents, or combinations of two agents. In particular, the combination of nitroglycerin or an .alpha.1-adrenergic blocker with sucralfate and **lidocaine** is particularly effective. Preparations of superior effectiveness combine an agent that relieves spasm of the IAS with a local **anesthetic** and with an agent with antiinflammatory and/or protective properties. 2) Nontoxic doses of alpha 1-adrenergic blockers, such as doxazosin, can. . . which by itself is intolerable by the rectal route of administration, becomes tolerable when given in combination with a local **anesthetic**. It thus can be a useful addition to a **composition** for the treatment of anorectal pain, as long as that **composition** contains a local **anesthetic** ingredient.

DETD A triple combination of nitroglycerin, sucralfate, and **lidocaine** (or more generally a nitrate, sucralfate, and a local **anesthetic**) will produce more rapid, complete, and long-lasting relief than a **composition** with only one or two of the three ingredients. A triple combination of an alpha 1-adrenergic blocker, sucralfate, and a local **anesthetic** will produce more rapid, complete and long-lasting relief than a **composition** with only one or two of the three ingredients. Despite the availability of all of these ingredients for many years,. . . nitroglycerin will have lesser side effects than an equally effective dose of nitroglycerin alone. Experience with the combination of nitroglycerin, **lidocaine**, and sucralfate suggests that it does have less side effects than nitroglycerin, either because less nitroglycerin is used by the. . .

CLM What is claimed is:

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker; and

applying an effective dose of the **composition** to the anal region.

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker and sucralfate; and applying an effective dose of the **composition** to the anal region.

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker and a local **anesthetic**; and applying an effective dose of the **composition** to the anal region.

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker, a local **anesthetic** and sucralfate; and applying an effective dose of the **composition** to the anal region.

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker, a local **anesthetic** and capsaicin; and applying an effective dose of the **composition** to the anal region.

10. The method of claim 3, 4 or 5, wherein the local **anesthetic** is selected from the group consisting of: **lidocaine**, **benzocaine**, **bupivacaine**, and **tetracaine**.

11. The method of claim 1, 2, 3, 4, or 5, wherein after the step of providing and before the step of applying, the method further comprises the step of: mixing the **composition** with a cream, gel, paste, lotion, ointment, aerosol, suppository, pad, liquid, emulsion, foam or, semisolid powder or a combination thereof.

. . .

12. The method of claim 1, 2, 3, 4, or 5 wherein the **composition** further comprises a cream, gel, paste, lotion, ointment, aerosol, suppository, pad, liquid, emulsion, foam or semisolid powder or a combination. . .

. . . patient with a painful condition of the anal region associated with muscle spasm, the method comprising steps of: providing a **composition** comprising an .alpha.-adrenergic blocker, a local **anesthetic** and sucralfate in a base of petrolatum, and further comprising a water soluble lubricant; and applying an effective dose of the **composition** to the anal region.

17. The method of claim 16 wherein the **composition** comprises approximately 0.1-1.0 milligrams of doxazosin or terazosin per 5 milliliters of **composition**, approximately 20-200 milligrams of **lidocaine** base per 5 milliliters of **composition**, and approximately 50-500 milligrams of sucralfate per 5 milliliters of **composition**.

18. The method of claim 16 wherein the local **anesthetic** is **lidocaine**.

L14 ANSWER 5 OF 45 USPATFULL
ACCESSION NUMBER: 1999:163855 USPATFULL

TITLE: Chemiluminescent compounds and methods of use
INVENTOR(S): Singh, Sharat, San Jose, CA, United States
Singh, Rajendra, Mountain View, CA, United States
Meneghini, Frank, Keene, NH, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Dade Behring Marburg GmbH, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6002000		19991214
APPLICATION INFO.:	US 1996-661849		19960611 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-373678, filed on 17 Jan 1995, now patented, Pat. No. US 5545834 which is a continuation of Ser. No. US 1992-916453, filed on 20 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ford, John M.
ASSISTANT EXAMINER: Kifle, Bruck
LEGAL REPRESENTATIVE: Leitereg, Theodore J
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1805
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD . . . Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tubercolosis hominis
Mycobacterium. . .

DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic

acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polynucleotide: a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD . . . context of the present invention, a ligand conjugated to a chemiluminescent label of this invention, is a ligand-label conjugate. A **composition** which is described as comprising subunit A conjugated to subunit B is a **composition** wherein subunit A is bound to subunit B.

DETD One embodiment of the present invention pertains to a chemiluminescent **composition** comprising a chemiluminescent compound of this invention in a pH 6-10 aqueous solution containing hydrogen peroxide or a means for. . . a hapten or an antibody, in the manner described above. Compound (I) is particularly suited for use in such a **composition**. If peroxide is to be detected, it will usually be desirable to have a relatively high concentration of the chemiluminescent. . .

DETD Another embodiment of the present invention is a light emitting chemical **composition** comprised of hydrogen peroxide and a chemiluminescent compound of this invention, for example, Compound (II). It is usually desirable to. . .

DETD . . . produce hydrogen peroxide as a function of the presence of the analyte, and (3) detecting the luminescence produced by the **mixture**; where the components may be added in any convenient order.

DETD . . . compound can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD . . . a chemiluminescent compound of this invention in a tube coated with antibodies to the HBsAg antigen. After incubation of the **mixture** for one hour, the tubes are washed and hydrogen peroxide is added. The emitted light intensity is related to the. . .

DETD One such kit comprises in packaged combination (1) a **composition** comprising a chemiluminescent compound of this invention, for example Compound (I), having bound thereto a specific binding pair member and. . . of hydrogen peroxide or an analyte that modulates the formation of hydrogen peroxide, and comprises in packaged combination (1) a **composition** comprising the compound A--L--Q described herein and (2) any ancillary reagents required to produce hydrogen peroxide from said analyte when. . .

DETD The reaction **mixture** was heated to 70.degree. C. with gentle stirring for 24 hours under argon. The solvent was evaporated under

vacuum to. . .

DETD . . . DMF, were added the carboxylate (3) (274 mg, 1.0 mmol) and carbonyl diimidazole (CDI) (225 mg, 1.5 mmol). The reaction **mixture** was stirred at room temperature for 16 hours. At this point, an aliquot of reaction **mixture** was found to be highly chemiluminescent when perborate (pH 9.5) was added. 1,2,4-Trihydroxybenzene (504 mg, 4.0 mmol) in 3 mL of acetonitrile was added to the above reaction **mixture**. The reaction was allowed to sit under argon for 12 hours. ##STR22## The solvent was evaporated under vacuum to obtain. . .

DETD . . . g, 48.1 mmol) in CH.sub.2 Cl.sub.2 (100 mL) was treated with methane sulfonyl chloride (3.6 mL, 46.5 mmol) and the **mixture** stirred until TLC indicated absence of starting material. The **mixture** was concentrated, adsorbed on alumina and chromatographed with a gradient of CH.sub.3 OH (0-5%) in CH.sub.2 Cl.sub.2 as the eluant.. . .

DETD . . . of (CH.sub.3 CH.sub.2).sub.3 N. ##STR24## The initial yellow solution, which rapidly turned almost colorless, was stirred for 14 hours. The **mixture** was concentrated and purified by preparative TLC (silica, CH.sub.2 Cl.sub.2 eluant) to yield 52 mg (60%) of the Compound (IIIa). . .

DETD . . . a vacuum oven at 50.degree. C. The .sup.1 H-NMR showed the crude to be a 4:1 (compound (8): compound (9)) **mixture** of isomers. Crystallization from boiling water afforded 4.10 g (56%) of the sulfonanilide (8) as tan flakes.

DETD . . . the sulfonanilide (8) (120 mg, 0.45 mmol). The initial yellow solution gradually turned almost clear, indicating adduct formation. The reaction **mixture** was concentrated after TLC indicated absence of starting materials. ##STR26## The concentrate was passed through silica (100 g, 10% CH.sub.3 CN in CH.sub.2 Cl.sub.2) and the higher R.sub.f (0.60-0.40) material, which was a **mixture** of two compounds, was collected. The **mixture** (260 mg) was dissolved in anhydrous DMF (20 mL) and treated with NaH (100 mg), batch-wise, allowing the initial effervescence to subside before subsequent additions. After 3 hours, the reaction **mixture** was quenched with 10% aqueous NH.sub.4 Cl (2 mL) and extracted with CH.sub.2 Cl.sub.2 (3.times.50 mL). The aqueous portion was. . .

DETD . . . to 0.degree. C. Methane sulfonyl chloride (1.8 mL), 19.0 mmol) was slowly added over a period of ten minutes. The **mixture** was stirred for 6 hours and allowed to attain room temperature over this period. The pyridine was distilled off after. . .

CLM What is claimed is:

5. A chemiluminescent **composition** comprised of the compound of claim 1 in a pH 6-10 aqueous solution containing hydrogen peroxide.

6. A light emitting chemical **composition** comprising hydrogen peroxide and a compound having the following formula: wherein: X' is O or S and Y' is N. . .

7. The **composition** of claim 6 which further comprises a catalyst.

L14 ANSWER 6 OF 45 USPATFULL

ACCESSION NUMBER: 1999:92783 USPATFULL

TITLE: Chemiluminescent compounds and methods of use

INVENTOR(S): Singh, Sharat, San Jose, CA, United States
Singh, Rajendra, Mountain View, CA, United States

	Meneghini, Frank, Keene, NH, United States Ullman, Edwin F., Atherton, CA, United States		
PATENT ASSIGNEE(S):	Dade Behring Marburg GmbH, Marburg, Germany, Federal Republic of (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5936070		19990810
APPLICATION INFO.:	US 1996-664269		19960611 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-373678, filed on 17 Jan 1995, now patented, Pat. No. US 5545834 which is a continuation of Ser. No. US 1992-916453, filed on 20 Jul 1992, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Ceperley, Mary E.		
LEGAL REPRESENTATIVE:	Leitereg, Theodore J		
NUMBER OF CLAIMS:	9		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 3 Drawing Page(s)		
LINE COUNT:	1818		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD . . . group

Hemophilus influenzae
H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis

Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polynucleotide: a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD . . . context of the present invention, a ligand conjugated to a chemiluminescent label of this invention, is a ligand-label conjugate. A **composition** which is described as comprising subunit A conjugated to subunit B is a **composition** wherein subunit A is bound to subunit B.

DETD One embodiment of the present invention pertains to a chemiluminescent **composition** comprising a chemiluminescent compound of this invention in a pH 6-10 aqueous solution containing hydrogen peroxide or a means for. . . a hapten or an antibody, in the manner described above. Compound (I) is particularly suited for use in such a **composition**. If peroxide is to be detected, it will usually be desirable to have a relatively high concentration of the chemiluminescent. . .

DETD Another embodiment of the present invention is a light emitting chemical **composition** comprised of hydrogen peroxide and a chemiluminescent compound of this invention, for example, Compound (II).

It is usually desirable to. . .

DETD . . . produce hydrogen peroxide as a function of the presence of the analyte, and (3) detecting the luminescence produced by the **mixture**; where the components may be added in any convenient order.

DETD . . . compound can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two,

hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD . . . a chemiluminescent compound of this invention in a tube coated with antibodies to the HBsAg antigen. After incubation of the **mixture** for one hour, the tubes are washed and hydrogen peroxide is added. The emitted light intensity is related to the. . .

DETD One such kit comprises in packaged combination (1) a **composition** comprising a chemiluminescent compound of this invention, for example Compound (I), having bound thereto a specific binding pair member and. . . of hydrogen peroxide or an analyte that modulates the formation of

hydrogen peroxide, and comprises in packaged combination (1) a **composition** comprising the compound A--L--Q described herein and (2) any ancillary reagents required to produce hydrogen peroxide from said analyte when. . .

DETD The reaction **mixture** was heated to 70.degree. C. with gentle stirring for 24 hours under argon. The solvent was evaporated under vacuum to. . .

DETD . . . DMF, were added the carboxylate (3) (274 mg, 1.0 mmol) and carbonyl diimidazole (CDI) (225 mg, 1.5 mmol). The reaction **mixture** was stirred at room temperature for 16 hours. At this point, an aliquot of reaction **mixture** was found to be highly chemiluminescent when perborate (pH 9.5) was added. 1,2,4-Trihydroxybenzene (504 mg, 4.0 mmol) in 3 mL of acetonitrile was added to the above reaction **mixture**. The reaction was allowed to sit under argon for 12 hours. ##STR23## The solvent was evaporated under vacuum to obtain. . .

DETD . . . g, 48.1 mmol) in CH.sub.2 Cl.sub.2 (100 mL) was treated with methane sulfonyl chloride (3.6 mL, 46.5 mmol) and the **mixture** stirred until TLC indicated absence of starting material. The **mixture** was concentrated, adsorbed on alumina and chromatographed with a gradient of CH.sub.3 OH (0-5%) in CH.sub.2 Cl.sub.2 as the eluant.. . .

DETD . . . of (CH.sub.3 CH.sub.2).sub.3 N. ##STR25## The initial yellow solution, which rapidly turned almost colorless, was stirred for 14 hours. The **mixture** was concentrated and purified by preparative TLC (silica, CH.sub.2 Cl.sub.2 eluant) to yield 52 mg (60%) of the Compound (IIIa). . .

DETD . . . a vacuum oven at 50.degree. C. The .sup.1 H-NMR showed the crude to be a 4:1 (compound (8): compound (9)) **mixture** of isomers. Crystallization from boiling water afforded 4.10 g (56%) of the

sulfonanilide (8) as tan flakes.

DETD . . . the sulfonanilide (8) (120 mg, 0.45 mmol). The initial yellow solution gradually turned almost clear, indicating adduct formation. The

reaction **mixture** was concentrated after TLC indicated absence of starting materials. ##STR27## The concentrate was passed through silica (100 g, 10% CH.sub.3 CN in CH.sub.2 Cl.sub.2) and the higher R.sub.f (0.60-0.40) material, which was a **mixture** of two compounds, was collected. The **mixture** (260 mg) was dissolved in anhydrous DMF (20 mL) and treated with NaH (100 mg), batch-wise, allowing the initial effervescence to subside before subsequent additions. After 3 hours, the reaction **mixture** was quenched with 10% aqueous NH.sub.4 Cl (2 mL) and extracted with CH.sub.2 Cl.sub.2

(3.times.50 mL). The aqueous portion was. . .

DETD . . . to 0.degree. C. Methane sulfonyl chloride (1.8 mL), 19.0 mmol) was slowly added over a period of ten minutes. The **mixture** was stirred for 6 hours and allowed to attain room temperature over this period. The pyridine was distilled off after. . .

CLM What is claimed is:
5. A chemiluminescent **composition** comprised of the compound of claim 1 in a pH 6-10 aqueous solution containing hydrogen peroxide.

6. A light emitting chemical **composition** comprising hydrogen peroxide and a compound having the following formula: ##STR33## wherein:
X' and Y' are linking groups each comprising. . .
7. The **composition** of claim 6, which further comprises a catalyst.

L14 ANSWER 7 OF 45 USPATFULL
ACCESSION NUMBER: 1998:72421 USPATFULL
TITLE: Method of separation employing magnetic particles and second medium
INVENTOR(S): Vorpahl, John, Livermore, CA, United States
PATENT ASSIGNEE(S): Dade Behring Marburg GmbH, Deerfield, IL, United States
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5770388		19980623
APPLICATION INFO.:	US 1993-168263		19931213 (8)

DISCLAIMER DATE: 20110118
RELATED APPLN. INFO.: Continuation of Ser. No. US 1989-455550, filed on 22 Dec 1989, now patented, Pat. No. US 5279936
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wolski, Susan
LEGAL REPRESENTATIVE: Jordan, Leland K, Rosenstock, Jerome, Leitereg, Theodore J.
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 1449
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods are disclosed for separating a component of interest from a **mixture** containing the component of interest and other components. The method comprises contacting a first liquid medium containing the component of. . .
SUMM . . . in which the material to be separated is intrinsically magnetic. On the other hand, one or more components of a **mixture** can be rendered magnetic by the attachment of a magnetically responsive entity. In biochemical separations, materials of interest are generally.
. .
SUMM . . . bearing poly-ADP-ribose synthetase on their surface from unbound polynucleosomes by causing specific antibodies to the synthetase
to bind, combining the **mixture** with gold-labeled protein A and separating by sucrose gradient velocity sedimentation whereupon the gold
bond polynucleosomes separated more rapidly. Courtoy,. . .
SUMM . . . Pat. No. 4,115,534. Functional magnetic particles formed by dissolving a mucopolysaccaride such as chitosan in acidified aqueous solution containing a **mixture** of ferrous chloride and ferric chloride is disclosed in U.S. Pat. No. 4,285,819. The microspheres may be employed to remove. . .
SUMM A diagnostic method employing a **mixture** of normally separable

protein-coated particles is discussed in U.S. Pat. No. 4,115,535. Microspheres of acrolein homopolymers and copolymer with hydrophilic.

.

.

SUMM . . . method of the present invention is directed to the separation of a component of interest from other components in a **mixture** by causing the binding of the component of interest to magnetic particles. Where the component of interest is present as. . . interactions. A first liquid medium containing the component of interest bound to magnetic particules and the other components of the **mixture** is contacted with, without mixing with, a second liquid medium that is of different density than and/or of different viscosity.

. .

SUMM One embodiment of a method in accordance with the present invention is a method for separating cells from a **mixture** containing the cells and other components. The method comprises layering a first liquid medium containing the cells and other components. . .

SUMM Component of interest (CI)--the compound or **composition** to be separated. The component of interest can be non-particulate or particulate. Non-particulate CI can be comprised of a member. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzoyl ecgonine, their derivatives and metabolites, ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, and their metabolites.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . Spore-forming Bacilli

	Phialophora jeanselmei
Bacillus anthracis	Microsporum gypseum
Bacillus subtilis	Trichophyton mentagrophytes
Bacillus megaterium	Keratinomyces ajelloi
Bacillus cereus	Microsporum canis
Anaerobic Spore-forming Bacilli	
	Trichophyton rubrum
Clostridium **botulinum**	Microsporum adouini
Clostridium tetani	Viruses
Clostridium perfringens	
	Adenoviruses
Clostridium novyi	Herpes Viruses
Clostridium septicum	Herpes simplex
Clostridium histolyticum	
	Varicella (Chicken pox)
Clostridium tertium	Herpes Zoster (Shingles)
Clostridium. . .	

SUMM Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a

molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

SUMM Polyionic reagent--a compound, **composition**, or material, either inorganic or organic, naturally occurring or synthetic, having at least two of the same charge, either polyanionic. . .

SUMM Releasing agent--a compound, **composition**, or material, either naturally occurring or synthetic, organic or inorganic, capable of reversing the non-specific binding between, i.e., dissociating, particulate. . .

SUMM . . . to magnetic particles is involved, such binding will usually occur essentially instantaneously, and it is usually sufficient to allow the **mixture** to stand for 60 sec., frequently less than 15 sec.; preferably the magnetic field is applied immediately after contacting of. . .

SUMM The invention further comprises a **composition** comprising (1) a first liquid medium containing magnetic particles to which are bound a component of interest (CI) and in. . . therewith (2) a second liquid medium having a different density and/or viscosity or immiscibility with the first liquid medium. The **composition** may further comprise a polyionic reagent of opposite charge to the magnetic particles. Alternatively, in the **composition** of the invention the magnetic particles can have a CI bound to an sbp member bound thereto.

CLM What is claimed is:

1. A method for the separation of a particulate biologic material (PBM) from a **mixture** containing said PBM and other components, which method comprises: combining in a first liquid medium said PBM and said other. . .

11. A method for separating cells from a **mixture** containing said cells and other components, which method comprises: combining in an aqueous medium said cells and said other components,. . .

L14 ANSWER 8 OF 45 USPATFULL

ACCESSION NUMBER:	1998:57716 USPATFULL
TITLE:	Aptamers specific for biomolecules and methods of making
INVENTOR(S):	Griffin, Linda, Atherton, CA, United States Albrecht, Glenn, Redwood City, CA, United States Latham, John, Palo Alto, CA, United States Leung, Lawrence, Hillsborough, CA, United States Vermaas, Eric, Oakland, CA, United States Toole, John J., Burlingame, CA, United States
PATENT ASSIGNEE(S):	Gilead Sciences, Inc., Foster City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5756291		19980526
APPLICATION INFO.:	US 1995-484192		19950607 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1992-934387, filed on 21 Aug 1992, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Zitomer, Stephanie W.		
LEGAL REPRESENTATIVE:	Bosse, Mark L.		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		

NUMBER OF DRAWINGS: 6 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 8242
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . ICAM, VCAM, E-selectin, thrombin, bradykinin, PGF2 and cell surface molecules. The technique involves complexation of the target molecule with a **mixture** of oligonucleotides containing random sequences and sequences which serve as primer for PCR under conditions wherein a complex is formed with the specifically binding sequences, but not with the other members of the oligonucleotide **mixture**. The complex is then separated from uncomplexed oligonucleotides and the complexed members of the oligonucleotide **mixture** are recovered from the separated complex using the polymerase chain reaction. The recovered oligonucleotides may be sequenced, and successive rounds. . .

SUMM . . . DNA complexes with the protein (in their case, the SP1 regulatory protein) were separated from the unbound oligomers in the **mixture** by band-shift electrophoresis and the complex oligonucleotides were rescued by PCR and cloned, and then sequenced using double-stranded mini-prep DNA. . .

DRWD FIG. 3 is a chart depicting aptamer sequences obtained from round 6 with 5-pentynyl dU in the **mixture** of oligomers in Example 20.

DETD . . . of glutamic acid from LTC4), LTE4 (resulting from the subsequent cleavage of glycine), LTF4 (an -glutamyl, cysteinyl derivative), SRS-A (a **mixture** of LTC4 and LTD4 known as the "slow-reacting substance of anaphylaxis"), HPETE (hydroperoxyeicosatetraenoic acid) and HETE (monohydroxyeicosatetraenoic acid). Eicosanoids are. . .

DETD As used herein, "aptamer" refers in general to either an oligonucleotide of a single defined sequence or a **mixture** of said oligonucleotides, wherein the **mixture** retains the properties of binding specifically to the target molecule. Thus, as used herein "aptamer" denotes both singular and plural. . .

DETD . . . Aptamers. In general, the method for preparing the aptamers of the invention involves incubating a desired target molecule with a **mixture** of oligonucleotides under conditions wherein some but not all of the members of the oligonucleotide **mixture** form complexes with the target molecules. The resulting complexes are then separated from the uncomplexed members of the oligonucleotide **mixture** and the complexed members which constitute an aptamer (at this stage the aptamer generally being a population of a multiplicity of oligonucleotide sequences) is recovered from the complex and amplified. The resulting aptamer (**mixture**) may then be substituted for the starting **mixture** in repeated iterations of this series of steps. When satisfactory specificity is obtained, the aptamer may be used as a. . . of the aptamer prepared. In this most generalized form of the method, the oligonucleotides used as members of the starting **mixture** may be single-stranded or double-stranded DNA or RNA, or modified forms thereof. However, single-stranded DNA is preferred. The use of. . .

DETD The oligonucleotides that bind to the target are separated from the rest of the **mixture** and recovered and amplified. Amplification may be conducted before or after separation from the target molecule. The oligonucleotides are conveniently. . .

DETD The starting **mixture** of oligonucleotide may be of undetermined

sequence or may preferably contain a randomized portion, generally including from about 3 to. . . 10 to 100 nucleotides. The randomization may be complete, or there may be a preponderance of certain sequences in the **mixture**, or a preponderance of certain residues at particular positions. Although, as described hereinbelow, it is not essential, the randomized sequence. . .

DETD The oligonucleotides of the starting **mixture** may be conventional oligonucleotides, most preferably single-stranded DNA, or may be modified forms of these conventional oligomers as described hereinabove.. . . may also be synthesized using solution phase methods such as triester synthesis, known in the art. The nature of the **mixture** is determined by the manner of the conduct of synthesis. Randomization can be achieved, if desired, by supplying mixtures of. . .

DETD . . . positions where randomization is desired. In general, the modification is included by use of a modified monomer in the synthesis **mixture**. Of course, any degree of randomization may be employed; some positions may be randomized by mixtures of only two or. . .

DETD In one embodiment of the method of the invention, the starting **mixture** of oligonucleotides subjected to the invention method will have a binding affinity for the target characterized by a Kd of 1 m or greater. Binding affinities of the original **mixture** for target may range from about 100M to 10M to 1M, but, of course, the smaller the value of the. . .

DETD Use of Modified Nucleotides and Oligonucleotides. In one embodiment of the invention method, the initial **mixture** of candidate oligonucleotides will include oligomers which contain at least one modified nucleotide residue or linking group.

DETD . . . reflect this characterization. If the modified form of cytosine (C*) is included in the PCR reaction as dC*TP, the resulting **mixture** will contain C* at positions represented by this residue in the original member of the candidate **mixture**. (It is seen that the PCR reaction cannot distinguish between various locations of C* in the original candidate; all C. . . would be understood that one or more of the positions now occupied by C was occupied in the original candidate **mixture** by C*, provided only one round of complexation/amplification is needed. If the amplified **mixture** is used in a second round, this new **mixture** must contain the modification.

DETD Thus, one preferred method comprises incubating the target with a **mixture** of oligonucleotides, wherein these oligonucleotides contain at least one modified nucleotide residue or linkage, under conditions wherein complexation occurs with some but not all members of the **mixture**; separating the complexed from uncomplexed oligonucleotides, recovering and amplifying the complexed oligonucleotides and optionally determining the sequence of the recovered. . .

DETD . . . based on the discovery that the presence of flanking sequences (usually primer binding sequences) on the oligonucleotides of the candidate **mixture** may limit aptamer structural diversity and/or inhibit binding, thereby resulting in less than the full range of structural variation that. . .

DETD (a) providing a **mixture** of oligonucleotides of unknown, non-predetermined or substantially non-predetermined, said **mixture** comprising a quantity of oligonucleotides sufficiently

reflective of the structural complexity of said target as to statistically ensure the presence. . .

DETD (b) incubating said **mixture** of oligonucleotides with said target under conditions wherein complexation occurs between some oligonucleotides and said target, said complexed oligonucleotides defining. . .

DETD In the first step, the oligonucleotides comprising the **mixture** way be of completely unknown sequence. The oligonucleotides comprising the pool also may be of partially known sequence, but without. . .

DETD . . . Preparation. It is often advantageous in enhancing the specificity of the aptamer obtained to remove members of the starting oligonucleotide **mixture** which bind to a second substance from which the target molecule is to be distinguished. This method is particularly useful. . . of selection and amplification will be conducted. In a positive/negative selection approach, the target will be incubated with the starting **mixture** of oligonucleotides and, as usual, the complexes formed are separated from uncomplexed oligonucleotides. The complexed oligonucleotides, which are now an. . .

DETD In an alternative approach, the negative selection step may be conducted first, thus mixing the original oligonucleotide **mixture** with the undesired substance to complex away the members of the oligonucleotide **mixture** which bind to the second substance; the uncomplexed oligonucleotides are then recovered and amplified and incubated with the target under conditions wherein those members of the oligonucleotide **mixture** which bind targets are complexed. The resulting complexes then removed from the uncomplexed oligonucleotides and the bound aptamer population is. . .

DETD In more detail, the oligonucleotide **mixture** is brought into contact with a first known cell line which is known to express a particular cell surface protein. . .

DETD The aptamer **mixture** is then incubated with the second (null) cell culture under similar conditions. The **mixture** brought into contact with a second cell line which is identical to the first cell line, except that the second. . .

DETD Modified Method Wherein Target/Aptamer Complexes are Separated from Solid Support. As set forth hereinabove, the original oligonucleotide **mixture** can be synthesized according to the desired contents of the **mixture** and can be separated by adding the oligonucleotide **mixture** to a column containing covalently attached target molecules (see, Ellington, A. D., et al., Nature (1990) 346:818-822) or to the. . .

DETD The oligomer **mixture** is added to and incubated with the support to permit oligonucleotide-target complexation. Complexes between the oligonucleotides and target molecule are. . .

DETD . . . "consensus sequence" means that certain positions, not necessarily contiguous, of an oligonucleotide are specified. By specified is meant that the **composition** of the position is other than completely random. Not all oligonucleotides in a **mixture** may have the same nucleotide at such position; for example, the consensus sequence may contain a known ratio of particular.

. . a consensus sequence might consist of a series of four positions wherein the first position in all members of the **mixture** is A, the second position is 25% A, 35% T and 40% C, the third position is T in all. . .

DETD . . . one or more additions, deletions or substitutions in the

nucleotide sequence, as long as a consensus sequence is conserved. A **mixture** of secondary aptamers may also function as target-specific aptamers, wherein the **mixture** is a set of aptamers with a portion or portions of their nucleotide sequence being random or varying, and a. . .

DETD (a) incubating said target with a **mixture** of member oligonucleotides under conditions wherein the target complexes with some, but not all members of the **mixture** to form oligonucleotide-target complexes;

DETD Another aspect of the invention (Method B) is directed to the method of Method A wherein said **mixture** of oligonucleotides contains at least one modified oligonucleotide.

DETD Another aspect of the invention (Method D) is directed to the method of Method B-C wherein said **mixture** of oligonucleotides contains one randomized-sequence region.

DETD . . . the invention (Method F) is directed to the method of Method B-E wherein the Kd with respect to the oligonucleotide **mixture** and target is at least 50-fold more than the Kd with respect to the aptamer and target.

DETD (a) incubating said target molecule with a **mixture** of oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD (a) incubating said target with a **mixture** of member oligonucleotides under conditions wherein the target complexes with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD wherein the dissociation constant (Kd) with respect to said target and **mixture** of oligonucleotides is less than about 20 nM, or

DETD . . . target is less by a factor of at least 50 as compared to the Kd

for said target and said **mixture** of oligonucleotides; or

DETD wherein said **mixture** of oligonucleotides consists of single-stranded DNA.

DETD (a) incubating the target molecule reversibly coupled to a support with a **mixture** of oligonucleotide sequences under conditions wherein the coupled target molecule complexes with some, but not all, members of the **mixture** to form support-bound oligonucleotide complexes;

DETD (d) optionally repeating steps (a)-(c) using as said **mixture** the recovered population of aptamers of step (c); and

DETD Another aspect of the invention (**Composition** A) is directed to a pharmaceutical **composition** for medical use comprising the aptamer of Aptamer A-I in admixture with a physiologically acceptable excipient.

DETD Another aspect of the invention (**Composition** B) is directed to a **composition** for diagnostic use which comprises the aptamer of Aptamer A-I.

DETD (a) incubating said target with a solution comprising a **mixture** of oligonucleotides under conditions where complexation occurs with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD (a) incubating said target with a solution comprising a **mixture** of oligonucleotides under conditions where complexation occurs with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD . . . X) is directed to the aptamer of Aptamer W wherein the extracellular protein is selected from the group consisting of **botulinum** toxin and diphtheria toxin, collagenase, tumor necrosis factor, antithrombin III, interleukins, elastase, and PDGF

(and) fibroblast growth factors.

DETD (a) incubating said target with a **mixture** of member oligonucleotides under conditions wherein the target complexes with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD Another aspect of the invention (Method Z) is directed to the method of Method Y wherein said **mixture** of oligonucleotides contains at least one modified oligonucleotide.

DETD Another aspect of the invention (Method AB) is directed to the method of Method Y-AA wherein said **mixture** of oligonucleotides contains at least one randomized-sequence region.

DETD . . . the invention (Method AD) is directed to the method of Method Y-AC wherein the Kd with respect to the oligonucleotide **mixture** and target is at least 50-fold more than the Kd with respect to the aptamer and target.

DETD (a) incubating said target molecule with a **mixture** of oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD (a) incubating said target with a **mixture** of member oligonucleotides under conditions wherein the target complexes with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD wherein the dissociation constant (Kd) with respect to said target and **mixture** of oligonucleotides is 1M, or

DETD . . . target is less by a factor of at least 50 as compared to the Kd for said target and said **mixture** of oligonucleotides; or

DETD wherein said **mixture** of oligonucleotides consists of single-stranded DNA.

DETD Another aspect of the invention (Method AG) is directed to the method of Method AF wherein said **mixture** of oligonucleotides contains at least one modified oligonucleotide.

DETD Another aspect of the invention (Method AI) is directed to the method of Method AF-AH wherein said **mixture** of oligonucleotides contains at least one randomized-sequence region.

DETD Another aspect of the invention (Method AK) is directed to the method of Method AF wherein said **mixture** of oligonucleotides is of unpredetermined sequence.

DETD (a) incubating the target molecule reversibly coupled to a support with a **mixture** of oligonucleotide sequences under conditions wherein the coupled target molecule complexes with some, but not all, members of the **mixture** to form support-bound oligonucleotide complexes;

DETD (d) optionally repeating steps (a)-(c) using as said **mixture** the recovered population of aptamers of step (c); and

DETD (a) incubating said target molecule with a **mixture** of oligonucleotides under conditions wherein complexation occurs with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD wherein said **mixture** of oligonucleotides contains at least one modified oligonucleotide.

DETD incubating said first target with a **mixture** of member oligonucleotides under conditions wherein complexation occurs with some,

but not all, members of said **mixture**;

DETD . . . second substance with said first aptamer population under conditions wherein complexation occurs with some, but not all, members of said **mixture**;

DETD contacting said second substance with a **mixture** of oligonucleotides under conditions wherein some but not all of the members of the **mixture** bind to the second substance;

DETD Another aspect of the invention (**Composition** C) is directed to a complex formed by a target molecule and the aptamer of Aptamer N-AX, AY, AZ, BA,. . .

DETD Another aspect of the invention (**Composition** D) is directed to a pharmaceutical **composition** for medical use comprising the aptamer of Aptamer N-AX, AY, AZ, BA, or BB in admixture with a physiologically acceptable. . .

DETD Another aspect of the invention (**Composition** E) is directed to a **composition** for diagnostic use which comprises the aptamer of Aptamer N-AX, AY, AZ, BA, or BB.

DETD Another aspect of the invention (**Composition** F) is directed to a conjugate for modulating immune response to a pathologic cell, comprising:

DETD Another aspect of the invention (**Composition** G) is directed to a conjugate according to **Composition** F wherein said targeting agent is selected from the group consisting of oligonucleotides, antibodies and ligands for cell surface receptors.

DETD Another aspect of the invention (**Composition** H) is directed to a conjugate according to **Composition** G wherein said targeting agent is the aptamer of Aptamer N-AX, AY, AZ, BA, or BB.

DETD Another aspect of the invention (**Composition** I) is directed to a conjugate according to **Composition** F wherein the immunomodulatory moiety is selected from the group consisting of peptides and carbohydrates.

DETD administering an amount effective to modulate immune response of a conjugate in accordance with **Composition** F.

DETD . . . substance, or a fragment of a target substance which method comprises incubating said target substance or said fragment with a **mixture** of randomized oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of said **mixture**;

DETD the improvement which comprises including in said **mixture** of randomized oligonucleotide sequences at least one modified nucleotide residue.

DETD Another aspect of the invention (Method BG) is directed to the method according to Method BD wherein said **mixture** of randomized oligonucleotide sequences is single-stranded DNA.

DETD Another aspect of the invention (**Composition** J) is directed to a complex which comprises a target substance or a fragment of a target substance and at. . .

DETD Another aspect of the invention (**Composition** K) is directed to the complex of **Composition** J wherein said at least one specifically-bound oligonucleotide is flanked by primer sequences adapted to permit application of PCR to said **mixture**.

DETD Another aspect of the invention (**Composition** L) is directed to the complex of **Composition** J with the proviso that the target is other than an oligonucleotide.

DETD . . . substance, or a fragment of a target substance which method comprises incubating said target substance or said fragment with a **mixture** of randomized oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of said **mixture**;

DETD wherein said **mixture** of randomized oligonucleotides includes

oligonucleotides containing at least one modified nucleotide residue.

DETD Another aspect of the invention (Method BJ) is directed to the method of Method BI wherein said **mixture** of randomized oligonucleotide sequences is single-stranded DNA.

DETD Another aspect of the invention (**Composition** M) is directed to a **mixture** of candidate aptamers comprising randomized nucleotide sequences, wherein said randomized sequences contain at least one modified nucleotide residue.

DETD Another aspect of the invention (**Composition** N) is directed to the **mixture** of **Composition** M wherein said randomized sequences are flanked by primer sequences adapted to permit application of PCR to said **mixture**.

DETD Another aspect of the invention (**Composition** O) is directed to the **mixture** of **Composition** M wherein said randomized sequences are single-stranded DNA.

DETD . . . any one of Aptamer BE-BH wherein the target molecule is a small molecule selected from the group consisting of -bungarotoxin, **botulinum** toxin and diphtheria toxin.

DETD (a) incubating said target with a **mixture** of member oligonucleotides under conditions wherein the target complexes with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD Another aspect of the invention (Method BL) is directed to the method of Method BK wherein said **mixture** of oligonucleotides contains at least one modified oligonucleotide.

DETD Another aspect of the invention (Method BN) is directed to the method of Method BK-BM wherein said **mixture** of oligonucleotides contains at least one randomized-sequence region.

DETD . . . the invention (Method BP) is directed to the method of Method BK-BO wherein the Kd with respect to the oligonucleotide **mixture** and target is at least 50-fold more than the Kd with respect to the aptamer and target.

DETD (a) incubating said target molecule with a **mixture** of oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD wherein said **mixture** of oligonucleotides contains at least one modified oligonucleotide base.

DETD (a) incubating said target with a **mixture** of member oligonucleotides under conditions wherein the target complexes with some, but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD wherein the dissociation constant (Kd) with respect to said target and **mixture** of oligonucleotides is 1M, or

DETD . . . target is less by a factor of at least 50 as compared to the Kd for said target and said **mixture** of oligonucleotides; or

DETD wherein said **mixture** of oligonucleotides consists of single-stranded DNA, and

DETD wherein said **mixture** of oligonucleotides contains at least one modified oligonucleotide base.

DETD Another aspect of the invention (Method BT) is directed to the method of Method BR-BS wherein said **mixture** of oligonucleotides contains at least one randomized-sequence region.

DETD Another aspect of the invention (Method BR) is directed to the method of

Method BR wherein said **mixture** of oligonucleotides is of unpredetermined sequence.

DETD (a) incubating the target molecule reversibly coupled to a support with a **mixture** of oligonucleotide sequences under conditions wherein the coupled target molecule complexes with some, but not all, members of the **mixture** to form support-bound oligonucleotide complexes;

DETD (d) optionally repeating steps (a)-(c) using as said **mixture** the recovered population of aptamers of step (c); and

DETD wherein said **mixture** of oligonucleotides contains at least one modified oligonucleotide base.

DETD (a) incubating said target molecule with a **mixture** of oligonucleotides under conditions wherein complexation occurs with some,

but not all, members of the **mixture** to form oligonucleotide-target complexes;

DETD wherein said **mixture** of oligonucleotides contains at least one modified oligonucleotide.

DETD incubating said first target with a **mixture** of member oligonucleotides under conditions wherein complexation occurs with some,

but not all, members of said **mixture**;

DETD . . . second substance with said first aptamer population under conditions wherein complexation occurs with some, but not all, members of said **mixture**;

DETD wherein said **mixture** of oligonucleotides comprises at least one modified base.

DETD contacting said second substance with a **mixture** of oligonucleotides under conditions wherein some but not all of the members of the **mixture** bind to the second substance;

DETD wherein said **mixture** of oligonucleotides comprises at least one modified base.

DETD Another aspect of the invention (**Composition** P) is directed to a complex formed by a target molecule and the aptamer of Aptamer BE-BH, CR, CS, CT,. . .

DETD Another aspect of the invention (**Composition** Q) is directed to a pharmaceutical **composition** for medical use comprising the aptamer of Aptamer BE-BH, CR, CS, CT, or CU in admixture with a physiologically acceptable. . .

DETD Another aspect of the invention (**Composition** R) is directed to a **composition** for diagnostic use which comprises the aptamer of Aptamer BE-BH, CR, CS, CT, or CU.

DETD Another aspect of the invention (**Composition** S) is directed to the aptamer of Aptamer BE-BH, CR, CS, CT, or CU coupled to an auxiliary substance.

DETD Another aspect of the invention (**Composition** T) is directed to the aptamer of **Composition** S wherein said auxiliary substance is selected from the group consisting of a drug, a toxin, a solid support, and. . .

DETD . . . to identify an oligonucleotide sequence which specifically binds a target substance, which method comprises incubating said target substance with a **mixture** of randomized oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of said **mixture**;

DETD the improvement which comprises including in said **mixture** of randomized oligonucleotide sequences at least one modified nucleotide residue.

DETD Another aspect of the invention (**Composition** U) is directed to

a complex which comprises a target substance and at least one specifically-bound oligonucleotide, which complex is. . .

DETD . . . to identify an oligonucleotide sequence which specifically binds a target substance, which method comprises incubating said target substance with a **mixture** of randomized oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of said **mixture**;

DETD wherein said **mixture** of randomized oligonucleotides includes oligonucleotides containing at least one modified nucleotide residue.

DETD Another aspect of the invention (**Composition** V) is directed to a **mixture** of candidate aptamers comprising randomized nucleotide sequences, wherein said randomized sequences contain at least one modified nucleotide residue.

DETD Another aspect of the invention (**Composition** W) is directed to the **mixture** of **Composition** V wherein said randomized sequences are flanked by primer sequences adapted to permit application of PCR to said **mixture**.

DETD incubating said kinin with a **mixture** of randomized oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of said **mixture**;

DETD Another aspect of the invention (Method CR) is directed to the method of Method CP wherein the oligonucleotide **mixture** is single-stranded DNA.

DETD Another aspect of the invention (**Composition** X) is directed to a **mixture** of oligonucleotide segments useful as a starting material in the recovery of an aptamer that specifically binds to a target kinin, which **mixture** comprises a randomized set of nucleotide sequences wherein each member of the set of said segments contains a random DNA. . .

DETD Another aspect of the invention (**Composition** Y) is directed to a complex which comprises a kinin target substance and its specifically bound oligonucleotide, which complex is. . .

DETD Another aspect of the invention (**Composition** Z) is directed to the complex of **Composition** Y wherein said target substance is bradykinin.

DETD incubating said hydrophobic target substance with a **mixture** of randomized oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of said **mixture**;

DETD Another aspect of the invention (Method DC) is directed to the method of Method CY wherein the oligonucleotide **mixture** is single-stranded DNA.

DETD Another aspect of the invention (**Composition** AA) is directed to a **mixture** of oligonucleotide segments useful as a starting material in the recovery of an aptamer that specifically binds to a target hydrophobic substance, which **mixture** comprises a randomized set of nucleotide sequences wherein each member of the set of said segments contains a random DNA. . .

DETD Another aspect of the invention (**Composition** AB) is directed to a complex which comprises a hydrophobic target substance and its specifically bound oligonucleotide, which complex is. . .

DETD Another aspect of the invention (**Composition** AC) is directed to the complex of **Composition** AB wherein said hydrophobic target substance is an eicosanoid.

DETD Another aspect of the invention (**Composition** AD) is directed to the complex of **Composition** AC wherein said eicosanoid is

selected from the group consisting of prostaglandins, thromboxanes, leukotrienes and prostacyclin.

DETD Another aspect of the invention (**Composition** AE) is directed to the complex of **Composition** AD wherein said eicosanoid is PGF2.

DETD . . . is directed to a process of any one of Method DO-DU wherein the oligonucleotides comprising said oligonucleotide pool are a **mixture** of at least 20-mers, 40-mers, 60-mers and 80-mers.

DETD . . . is directed to a process of any one of Method EC-EI wherein the oligonucleotides comprising said oligonucleotide pool are a **mixture** of at least 20-mers, 40-mers, 60-mers and 80-mers.

DETD Another aspect of the invention (**Composition** AF) is directed to a conjugate for modulating immune response to a pathologic cell, comprising:

DETD Another aspect of the invention (**Composition** AG) is directed to a conjugate according to **Composition** AF, wherein said targeting agent is selected from the group consisting of oligonucleotides, antibodies and ligands for cell surface receptors.

DETD Another aspect of the invention (**Composition** AH) is directed to a conjugate according to **Composition** AF, wherein the immunomodulatory moiety is selected from the group consisting of peptides and carbohydrates.

DETD Another aspect of the invention (**Composition** AI) is directed to a conjugate according to **Composition** AF, wherein the immunomodulatory moiety is a peptide incorporating a sequence derived from an immunogenic protein of viral or bacterial. . .

DETD Another aspect of the invention (**Composition** AJ) is directed to a conjugate according to **Composition** AF, wherein the immunomodulatory moiety elicits a cytotoxic lymphocyte response.

DETD Another aspect of the invention (**Composition** AK) is directed to a conjugate according to **Composition** AJ, wherein the immunomodulatory moiety is cyclosporin A or interleukin-6.

DETD administering an amount effective to modulate immune response of a conjugate in accordance with **Composition** AF.

DETD . . . first set of cells having a set of surface materials including said complexation target on the cell surface with a **mixture** of randomized oligonucleotide sequences under conditions wherein complexation occurs with some, but not all, members of said **mixture**;

DETD Another aspect of the invention (Method FP) is directed to the method of Method FB wherein the oligonucleotide **mixture** is single-stranded DNA.

DETD . . . FS) is directed to a process for recovering cells which express a target molecule on the surface thereof from a **mixture** of cells some of which cells do not express the target molecule, comprising the steps of:

DETD contacting a first set of cells having a specific target molecule on their surface with a randomized **mixture** of oligonucleotide sequences under conditions wherein some but not all of the sequences will bind to the cellular surfaces;

DETD contacting the labeled sequences with the **mixture** of cells and determining which cells have the labeled sequences bound thereto; and

DETD contacting a first set of cells having a specific target molecule on their surface with a randomized **mixture** of oligonucleotide sequences under conditions wherein some, but not all of the sequences

will bind to the cellular surfaces;
DETD (a) incubating the target substance reversibly coupled to a support with
a **mixture** of randomized oligonucleotide sequences under conditions wherein the coupled target substance complexes with some, but
not all, members of the **mixture** to form support-bound aptamer-target complexes;
DETD (a) incubating the target substance reversibly coupled to a support with
a **mixture** of randomized oligonucleotide sequences under conditions wherein the coupled target substance complexes with some, but
not all, members of the **mixture** to form support-bound aptamer-target complexes;
DETD . . . in dioxane and converted to the N-hydroxy-succinimide (NHS) ester by treatment with NHS and diisopropyl carbodiimide for 24 hrs. This **mixture** was then added to 1 ml of the settled support Toyopearl washed previously with 200 mM NaHCO.sub.3. The **mixture** was shaken for 24 hrs., and washed with a NaHCO.sub.3 solution. To determine the amount of coupling, the above described. . .
DETD . . . dissolved in dioxane and converted to the NHS-ester by treatment with N-hydroxy-succinimide (NHS) and diisopropyl carbodiimide for 24 hrs. This **mixture** is then added to a toyopearl AF-amino 650M (Toyo Haas, Inc.) support (1 ml of settled support) which has been washed previously with 200 mM NaHCO.sub.3). The **mixture** is shaken for 24 hours and the support is washed with 200 mM NaHCO.sub.3 solution. To determine the amount of. . .
DETD . . . production by about 70 to 95%. A control plate of IL-1R cells incubated with labeled selected aptamer alone and in **mixture** with the initial pool of unselected aptamer is included to demonstrate that binding is specific for the IL-1Rm molecule. Little. . .
DETD . . . X (Haematologic Technologies Inc, Cat No. HCXA-0060). After shaking overnight to permit Factor X binding to the Con-A beads, the **mixture** was briefly centrifuged and the supernatant removed. The beads were resuspended in fresh selection buffer and transferred to a column. . .
DETD . . . g (6.25 nmole) thrombin (Sigma, Cat. no. T-6759). After shaking
overnight to permit thrombin binding to the Con-A beads, the **mixture** was briefly centrifuged and the supernatant removed. The beads were resuspended in fresh selection buffer and transferred to a column. . .
DETD . . . presence of 0.08 mole of radiolabeled 96-mer derived from cloned Round 5 aptamer DNA. After incubation, the thrombin and aptamer **mixture** was applied to nitrocellulose filters (0.2 micron, 2.4 cm diameter) that were pretreated with salmon sperm DNA (1 mg/ml DNA in selection buffer) and washed twice with 1 ml selection buffer. After application of thrombin **mixture**, the filters were washed three times with 1 ml selection buffer. The radioactivity retained on the filters was then determined.. . .
DETD . . . thrombin activity was studied using a consensus-related sequence 7-mer, 5' GGTTGGG 3', or a control 7-mer with the same base **composition** but different sequence (5' GGGGGTT 3'). Clotting times were measured using the timer apparatus as above. The thrombin clotting time. . .
DETD . . . compound is converted to the triphosphate form and tested in the PCR assay described in Example 1 using an appropriate **mixture** of three normal deoxytriphosphates or ribotriphosphates along with a single modified base analog.

DETD . . . 1 nM was incubated with the indicated protein for several minutes at room temperature, followed by filtration of the aptamer-protein **mixture** through a nitrocellulose filter. The filter was washed with 3 mL of selection buffer and then radioactivity bound to the. . .

DETD . . . 10 L ancrod solution was added to 95 L of selection buffer prewarmed to 37 C. 100 L of this **mixture** was transferred to the coagulation cup of the fibrometer described above, followed by addition of 200 L of fibrinogen and. . .

DETD . . . described in Example 6 above, was used. Young adult rats of mixed gender and strain were used. The animals were **anaesthetized** and a diester of the 15-mer was injected through a catheter in 200 l volumes (in 20 mM phosphate buffer,. . .

DETD . . . PT assay was conducted using 0.1 mL of monkey plasma prewarmed to 37 C. and 0.2 mL of a 1:1 **mixture** of thromboplastin (used according to manufacturers instructions) and CaCl.sub.2 (25 mM), also prewarmed to 37 C. Thrombin clot times were. . .

DETD . . . Technologies Inc.) and human fibrinogen pre-equilibrated at 37 C. was added. The final concentration of thrombin and fibrinogen in the **mixture** was 13 nM and 5.9M respectively. Oligonucleotides concentrations were as listed above and were at/or greater than their respective Kd. . .

DETD . . . from bFGF peak was brought to 0.1% SDS concentration and 20 mM ethylenediaminetetraacetic acid (EDTA), vortexed and extracted with a **mixture** of 180 L phenol and 180 L chloroform. The volume reduced to about 250 L. The resulting material was diluted. . .

DETD . . . Inc, Cat No. HCXA-0060). After shaking overnight at 4 C. to permit Factor X binding to the Con-A beads, the **mixture** was briefly centrifuged and the supernatant removed. The beads were resuspended in fresh selection buffer and transferred to a column. .
.

DETD . . . procoagulant activity prior to replipidation. The apoprotein was relipidated by incubation at 37 C. for 30 min in a relipidation **mixture** containing 800 L of TBSA (50 mM tris HCl, pH 7.5, 100 mM NaCl, 0.1% BSA) and 50 L of. . .

DETD . . . protein and
RLF1 protein)
early gene products (including SMLF1, MRF1, ALF2, HRF1,
ribonucleotide reductase, thymidine kinase [XLF1])
virus-encoded glycoproteins
lipopolysaccharides (from gram negative or grain positive
bacteria)
botulinum toxin
diphtheria toxin
cholera toxin
endotoxin
D. Intracellular Targets (proteins/lipids/Enzymes
Lipids
fatty acids
glycerides
glycerylethers
phospholipids
sphingolipids
steroids
fat soluble vitamins
glycolipid
phospholipids
lecithins
phosphatidic acids (cephalins)
sphingomyelin

plasmalogens
phosphatidyl inositol
phosphatidyl choline
phosphatidyl serine
phosphatidyl inositol
diphosphatidyl glycerol
oleic
palmitic
stearic acids
linoleic acid
acylcoenzyme A
phosphoglyceride
phosphitidate
retinoic acid
retinoids
lipoprotein. . . Other Compounds
2-phosphoglycerate
3-hydroxy acyl-CoA
3-phospho-5-pyrophosphomevalonate
3-phosphoglycerate
3-phosphohydroxypyruvate
3-phosphoserine
5-alpha-dihydrotestosterone
5-phospho-beta-ribosylamine
5-phosphoribosyl 1-pyrophosphate
5-phospho-alpha-ribosyl-1-pyrophosphate
5-phosphoribosyl-4-carboxamide-5-aminoimidazole
6-benzylaminopurine
17-hydroxyprogesterone
acetominophen
aceyt-coenzyme A
acetylcholine
acetylsalicylic acid
adenine
adenosine
ADP
aflatoxin B1
aflatoxin G1
aflatoxin M1
aldosterone
allantoin
allodeoxycholic acid
allopurinol
alpha ketoglutarate
alpha,beta-dihydroxy-beta-methylvalerate
alpha-aceto-alpha-hydroxybutyrate
alpha-amino-beta-ketoadipate
alpha-bungarotoxin
alpha-carotine
alpha-keto-beta-methylvalerate
alpha-ketoglutarate
alpha-ketobutyrate
alpha-ketoglutarate
amiloride
aminopterin
AMP
amylopectin
amylose
anti-diuretic hormone
antipyrine

arachidic acid
arachidonic acid
arecoline
arginine
argininosuccinate
ascorbic acid
aspartate semialdehyde
aspartyl phosphate
ATP
atropine
bacitracine
benztropine
beta-caratine
betamethazone
bilirubin
biliverdin
biotin
carbachol
carbamoyl phosphate
carboline
carnitine
CDP
cholesterol
cholic acid
chorismic acid
cis aconitate
citrate
citrulline
CMP
cocaine
codeine
Coenzyme Q
coenzyme A
corticosterone
cortisol
cortisone
coumarin
creatine
creatinine
CTP
cyanocobalamin
cyclic AMP
cyclic CMP
cyclic GMP
cyclic TMP
cystathionine
cytnidine
cytochrome
D-Erythrose
D-Fructose
D-Galactosamine
D-glucose
D-Glucuronic acid
dADP
dAMP
dATP
dCDP
dCMP
dCTP
delta-4-androstenedione

deoxyadenosyl cobalamin
deoxycholic acid
dGDP
dGMP
dGTP
dihydroorotate
dihydroxyphenylalanine
diphosphoglycerate
dopanane
dTDP
dTMP
dTTP
dUDP
dUMP
dUTP
eosinophil chemotactic factor of anaaphyaxis-A
epinephrine
estriol
esdone
ethynylestrdiol
FAD
farnesyl pyrophosphate
fatty Acyl-s-CoA
ferrodoxin
FMN
FMNH2
folic acid
fructose 2,6-diphosphate
fructose
fructose 1,6-diphosphate
fructose 6-phosphate
Fructosel,6-diphosphate
fumarate
galactose
galactose
GalNAC
gama-aminolevulinate
gamma-carotene
gastric inhibitory protein
gaunidinoacetate
GDP
gentamycin
glucosamine
glucosamine 6-phosphate
glucose
glucose 1,6-diphosphate
glucose 1-phosphate
glucose 6-phosphate
Glutamate
glutamate semialdehyde
glutaryl-CoA
glutathione
glyceraldehyde 3-phosphate
glycerol 1-phosphate
glychocholate
glycine
glyoxylate
GMP
GTP
guanine

hemichohne
histamine
homogentisate
homoserine
hydrocortisone
hydroxyproline
indole
inosine
inositol
inositol phosphate
intermediate molecular weight eosinophil chemotactic
factor. . .

L14 ANSWER 9 OF 45 USPATFULL

ACCESSION NUMBER:	1998:6916 USPATFULL
TITLE:	Photoactivatable chemiluminescent matrices
INVENTOR(S):	Pease, John S., Los Altos, CA, United States Kirakossian, Hrair, San Jose, CA, United States Wagner, Daniel B., Sunnyvale, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syntex (U.S.A.) Inc., San Jose, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5709994		19980120
APPLICATION INFO.:	US 1995-470862		19950606 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1992-923069, filed on 31 Jul 1992		

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Myers, Carla J.
LEGAL REPRESENTATIVE:	Finnegan, Henderson, Farabow, Garrett & Dunner
NUMBER OF CLAIMS:	74
EXEMPLARY CLAIM:	1
LINE COUNT:	3237

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . presence of the analyte and determining whether the sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties. Upon activation of the photosensitizer property singlet oxygen is generated and activates the chemiluminescent. . .

SUMM U.S. Pat. No. 4,311,712 (Evans, et al.) discloses a process for preparing a freeze dried liposome **mixture**.

SUMM . . . in a fluidic system, (c) wear in a mechanical part or (d) emission of light. The method comprises irradiating a **composition** arising from or subject to the condition. The **composition** comprises a non-particulate solid matrix or a particulate matrix having incorporated therein (a) a photosensitizer capable upon irradiation of generating. . .

SUMM . . . aspect of the present invention concerns a method for generating delayed luminescence. The method comprises the step of irradiating a **composition** comprising a non-particulate, solid matrix or particulate solid or fluid matrix having incorporated therein (1) a photosensitizer capable upon irradiation. . .

SUMM . . . presence of the analyte and determining whether the sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties such that upon activation of the photosensitizer property singlet oxygen is

generated and activates. . .

SUMM . . . of containing said analyte, (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both photosensitizer and chemiluminescent properties such that upon activation of the photosensitizer property singlet oxygen is generated and activates. . .

SUMM Another embodiment of the invention is a **composition** comprising a non-particulate solid matrix or particulate solid or fluid having incorporated therein a photosensitizer capable upon activation of generating. . .

SUMM Another **composition** in accordance with the invention comprises a particle, either solid or fluid, having incorporated therein a photosensitizer capable of generating. . .

SUMM Another embodiment of the invention is a **composition** comprising fluid particles selected from the group consisting of oil droplets, liposomes and emulsions having incorporated therein a photosensitizer capable. . .

SUMM Another embodiment of the present invention is a method for calibrating light intensity emitted by a luminescent **composition**, The method comprises the steps of (a) combining in a medium a luminescent **composition** capable of emitting light upon irradiation and one of the above compositions of the invention, wherein one of the compositions. . . for light emission substantially greater than the decay time for the other, (b) irradiating the medium to activate the luminescent **composition** and the **composition** of the invention, (c) measuring the intensity of light emitted during the decay of the activated **composition** having the shorter decay time, (d) measuring the intensity of light emitted after the measuring of step (c) and after at least partial decay of the activated **composition** having the shorter decay time, and (e) comparing the intensity of the light emitted during the decay of the activated **composition** having the shorter decay time with the intensity of light emitted in step (d) to provide for internal calibration. Steps b and c may be repeated one or more times prior to step d. In one embodiment the activated **composition** of **composition** of the invention has the shorter decay time. Another embodiment of the present invention is a kit comprising one of. . .

SUMM . . . lifetime of the luminescent decay is determined by a number of factors including the structure of the chemiluminescent compound, the **composition** of the solid material or the particle, the temperature and the presence of activators that enhance the rate of decomposition. . .

SUMM . . . gas. Application of tracers to detect leaks is well-known in the art. In general, about 10.sup.-14 -10.sup.-2 % of a **composition** of the invention is dispersed into the liquid or gas. Next, the fluid is irradiated with light to activate the. . .

SUMM . . . reaction of singlet oxygen with the chemiluminescent compound to be sufficiently stable so that luminescence will not occur until the **composition** is heated. Preferably, for these applications the **composition** is in the form of a film. The compositions may also be used to calibrate light sources and photometric devices.. . .

SUMM . . . where they can be used as a label or as part of a labeled reagent. For the most part the **composition** will have a member of a specific binding pair (sbp) bound to its surface. The sbp member may be capable. . .

SUMM Where the molecule to be detected involves a cell, the cell can be labeled with a particulate **composition** of the invention. For

example, the **composition** of the invention can include an sbp member complementary to an sbp member on the surface of the cell. The. . .

SUMM The present compositions can be utilized for internal calibration in luminescent assays. By including particles of the **composition** in an assay medium in which luminescence is produced by irradiating the medium, the **composition** produces an emission that can be detectably different from that produced in the assay. This difference can be the result. . .

SUMM . . . a fluorescence immunoassay the fluorescence intensity is measured first. Irradiation of the medium is discontinued and luminescence emanating from the **composition** of the invention is measured to provide an accurate internal reference of light intensity, detector sensitivity and sample interference. The. . . the measurement. Following the final cycle, the intensity of light which will now be emanating primarily from the present particulate **composition** can be independently measured because the decay times for the present particulate compositions are much longer. The residual light intensity. . . can be ratioed against the residual intensity of the present particulate compositions to provide for internal calibration. Conversely the present **composition** decay times could be shorter than the '490 **composition** decay times and the same procedure could be used for calibration except that the rapidly decaying light intensity would serve. . .

SUMM An assay for an analyte may be accomplished by separating a particulate **composition** of the invention used as a label, to which has become bound an analyte or an sbp member whose presence is indicative of the presence of an analyte, from unbound **composition**. Either the separated bound or unbound fraction is treated to activate the photosensitizer, usually by irradiation with light, and the. . .

SUMM Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

SUMM . . . Spore-forming Bacilli

	Phialophora jeanselmei
Bacillus anthracis	Microsporum gypseum
Bacillus subtilis	Trichophyton mentagrophytes
Bacillus megaterium	Keratinomyces ajelloi
Bacillus cereus	Microsporum canis
Anaerobic Spore-forming Bacilli	
	Trichophyton rubrum
Clostridium **botulinum**	Microsporum adouini
Clostridium tetani	Viruses
Clostridium perfringens	Adenoviruses
Clostridium novyi	Herpes Viruses
Clostridium septicum	Herpes simplex
Clostridium histolyticum	Varicella (Chicken pox)
Clostridium tertium	Herpes Zoster (Shingles)

Clostridium. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeins, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms,

which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and metabolites of the above.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

SUMM Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

SUMM . . . the most part, when a linking group is bound to the photosensitizer, the photochemically activatable chemiluminescent compound or a particulate **composition** of the invention will have a non-oxocarbonyl group including nitrogen and sulfur analogs, a phosphate group, an amino group, alkylating. . .

SUMM . . . the above functionalities can also be utilized as attaching groups, which permit attachment of an sbp member to a particulate **composition** comprised of the photosensitizer and chemiluminescent compound.

SUMM . . . chemical reagents is required to activate the present compositions and the photosensitizer and the chemiluminescent compound are found within one **composition**.

SUMM . . . case these compounds will preferably be hydrophobic to reduce their ability to dissociate from the particle. In general the particle **composition** is chosen so as to favor association of the photosensitizer and the chemiluminescent compound with the particle.

SUMM . . . surfactant is present in from about 0.1 to 5, more usually from about 0.1 to 2 weight percent of the **mixture** and subjecting the **mixture** in an aqueous medium to agitation, such as sonication or vortexing. Illustrative lipophilic compounds include hydrocarbon oils, halocarbons including fluorocarbons,. . .

SUMM . . . frequently comprised of phospholipids. Phospholipids employed in preparing particles utilizable in the present invention can be any phospholipid or phospholipid **mixture** found in natural membranes including lecithin, or synthetic glyceryl phosphate diesters of saturated or unsaturated 12-carbon or 24-carbon linear fatty. . .

SUMM . . . a variety of methods, including a method described by Olsen, et al., Biochemica et Biophysica Acta, 557(9), 1979. Briefly, a **mixture** of lipids containing the appropriate compound(s) in an organic solvent such as chloroform is dried to a thin film on. . .

SUMM . . . CC can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

SUMM . . . particles in accordance with the present invention. Polystyrene particles (175 nm) are prepared by heating in the presence of a **mixture** of both photosensitizer and CC. The medium employed is a **mixture** of water, ethylene glycol, and benzyl alcohol in the approximate ratio of 1:8:1 by volume. This **mixture** provides a balance of both aqueous and organic properties. A water-like solvent is preferred to maintain the colloidal stability of. . .

SUMM . . . CC are separately prepared as solutions (5 mM) in benzyl alcohol. Aliguots in varying ratios are then added to a **mixture** of ethylene glycol, benzyl alcohol 9:1 by volume and the **mixture** heated to 100 to 110.degree.. Appropriate aliguots of the particles, into which the photosensitizer and the CC are to be incorporated, are then added to the hot **mixture** while stirring vigorously. Heating is continued briefly and then the **mixture** is cooled and diluted with ethanol. Excess dye and solvent **mixture** are removed by repeated centrifugation. Finally, the washed particles are resuspended in a convenient volume of water (generally 100 mg. . .

SUMM . . . containing an analyte and (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both a photosensitizer and a CC. Conditions are chosen such that an sbp member complex is formed in relation. . .

SUMM Another factor that allows for control of the time to luminescence is the **composition** or the particle. In general, when the particle is composed of a non-polar material in which the CC is dissolved. . .

SUMM . . . formed in relation to the presence of the analyte and determining whether the sbp member complex has formed. A particulate **composition** of the invention is employed as a label to assist in the determination. An sbp member complex involving the label reagent is formed in relation to the presence of analyte in the medium. The **composition** is then irradiated with light and light energy from the chemiluminescent compound is measured such as, for example, by visual. . .

SUMM Another aspect of the present invention is a **composition** comprising a solid matrix having incorporated therein a photosensitizer capable upon activation of generating singlet oxygen and a chemiluminescent compound. . . compound can be covalently linked to the matrix or can be associated with the matrix with no covalent bounds.

The **composition** can comprise one or a plurality of distinct chemiluminescent compounds and one or a plurality of distinct photosensitizers and can. . . energy from the chemiluminescent compound. The distinct chemiluminescent compounds may differ by differing rates of activation by singlet oxygen. The **composition** may also comprise an activator that may or may not be fluorescent and that enhances the decay of an activated chemiluminescent compound. The **composition** can further comprise a member of a specific binding pair (sbp) bound thereto wherein the **composition** is usually particulate.

SUMM Another aspect of the present invention is a **composition** comprising a particle having incorporated therein a photosensitizer capable of generating singlet oxygen and a chemiluminescent compound capable of being. . .

SUMM . . . above. The amount of Reagent 1 is sufficient to provide a concentration of antibody of about 10.sup.-8 molar. The reaction **mixture** is then added to the microtiter plate well (Reagent 2) and incubated for a period of one hour at 25.degree. C. The reaction **mixture** is then removed from the well and the plate is washed with a buffered aqueous medium at pH 8.0 and. . . TSH to determine the concentration of TSH in the unknown. Alternatively, following incubation and removal from the well, the reaction **mixture** containing unbound latex particles is similarly irradiated, and the amount of light emitted from the system is measured and compared. . .

SUMM . . . containing an anti .alpha.-chain antibody labeled with fluorescein and an anti hCG .beta.-chain antibody labeled with biotin. After incubating the **mixture** for 10 minutes, there is added to the **mixture** 200 .mu.L of a suspension containing 2 .mu.g of each of the above beads and 1 .mu.g of 180 nm. . . the present

invention) containing both chlorophyll and 1-phenyl-2-p-dimethylaminophenyl-5,6-dihydro-1,4-dioxene, a chemiluminescent acceptor that decays with a 2 minute half life. The **mixture** is incubated for 10 minutes and then irradiated for one second with a tungsten-halogen lamp equipped with a 650 nm. . .

SUMM . . . be combined in one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises a **composition** comprising a suspendible particle having associated therewith a chemiluminescent compound and a photosensitizer, the particle having an sbp member bound. . .

DETD . . . (nC.sub.10 PC) (particle preparations A, B, C, D, respectively) and 10 ul C.sub.18 benzal acridan were mixed together and the **mixture** was heated to 100.degree. to 110.degree. C. for 1 min. Then, 0.1 ml of 0.716.mu. CML was added to the **mixture**, which was heated for 5 min at 100.degree. to 110.degree.. The **mixture** was allowed to cool to room temperature. Equal volumes of ethanol were added and the **mixture** was centrifuged at 15K for 30 min. The centrifugate was decanted and the particles were combined with 2 ml of. . .

DETD . . . nC.sub.10 PC (10, 25, or 50 .mu.l). Heating was continued for 10 min. An effort was made to keep the **mixture** just slightly below the boiling point of the water, but occasionally boiling was observed.

DETD . . . 10 .mu.g/ml in 0.1M Tris 0.3M NaCl, 25 mM EDTA, 1 mg/ml BSA pH 8.2. 0.1 ml of this diluted **mixture** was illuminated with a halogen lamp fitted with a 610 nm long pass filter for 60 sec. The first 20. . .

DETD . . . Chemical Co.) (3.22 g, 28 mmole) was added as a solid to the DMF solution and allowed to dissolve. The **mixture** was then cooled in an ice bath. Dicyclohexylcarbodiimide (Aldrich Chemical Co.) (5.8 g, 28 mmole) was dissolved in dry DMF (10 ml) and added all at once to the cold DMF solution. The **mixture** was stirred at ice bath temperature for 30 min. and then allowed to come to room temperature. The course of. . .

DETD 4,9-Dioxa-1,12-dodecane diamine (25.5 g, 125 mmole) was diluted with dry DMF (10 ml). The fluorescein NHS ester reaction **mixture** was cooled in ice under an argon atmosphere and the diamine solution added dropwise over a period of 5 minutes.. . . The course of the reaction was followed by tlc using the above system. When the reaction was judged complete, the **mixture** was diluted with water (100 ml) and cooled in ice to precipitate dicyclohexylurea, which was removed by filtration.

DETD . . . solution. Diglycolic anhydride (Aldrich Chemical Co.) (101 mg, 0.87 mmole) was dissolved in 1 ml DMF and added to the **mixture**. An additional 25 mg of diglycolic anhydride was added to force the reaction to completion as judged by silica gel. . .

DETD . . . prepared as described above in Part C) with 12 mg of dicyclohexylcarbodiimide (DCC) (in 100.mu. of anhydrous DMF). The reaction **mixture** was stirred gently at room temperature for 5 hours in a tightly closed vial. Then, the reaction **mixture** was filtered through glass wool to remove cyclohexylurea (side product of this reaction). The filtered reaction **mixture** was extracted with 2 ml of hexane (to remove unreacted DCC). The formation of F-LC.sub.19 -NHS was confirmed by TLC. . .

DETD . . . NaCl/pH7.6 with 20.mu. of anhydrous DMF containing F-LC.sub.19 -NHS (IgG:F-LC.sub.19 -NHS.tbd.1:20) at room temperature for 2 hrs. Then, the reaction **mixture** was purified by Sephadex G-25 (1.5.times.20 cm) column equilibrated in 0.02M NaPi, 0.15M NaCl, pH7.4. The hapten number was determined. . .

DETD . . . small aliquot used for the reaction) were mixed together and incubated for three hours at 4.degree. C. In the reaction **mixture**, the molar ratio of the reactants was Ab.sub.1 :Biotin-LC.sub.7 -NHS=1:25. The uncoupled biotin was removed by Sephadex.RTM. G-25 column. The. . .

DETD . . . 15 mL of 0.02M Borax (Sigma Chemical Company), 0.08M NaCl, 2 mg/mL 3G1 IgG(Ab.sub.F), and 8 mg/mL BSA/pH 8.9. The **mixture** was gently mixed (no stirring) overnight at 4.degree. C. The remaining reactive groups on the beads (if any) were blocked. . .

DETD . . . Ab.sub.1 -biotin and 1 .mu.g/mL Ab.sub.2 -fluorescein (9G3) in assay buffer (0.05M NaPi, 0.15M NaCl, 4 mg/mL BSA/pH 7.6). This **mixture** was incubated at room temperature for 1 hour. To this **mixture** 100 .mu.L of 1M Na.sub.3 Citrate/pH 7.17 was added, followed by 100 .mu.L of 1.0 mg/mL Ab.sub.F -bead in assay. . . from the unbound fraction by 0.5 cm glass beads coated with avidin (one glass bead per tube used). The assay **mixture** was incubated with the glass beads for 2.5 hours at room temperature (shaking in dark). After incubation, each glass bead. . .

CLM What is claimed is:

1. A method for determining the presence or absence of an analyte, said method comprising: irradiating a **composition** suspected of containing the analyte, said **composition** comprising a non-particulate solid matrix or a particulate matrix, said matrix having incorporated therein (1) a photosensitizer that upon irradiation. . .

8. A method for generating delayed luminescence, said method comprising the step of irradiating a **composition** comprising a solid or particulate matrix having incorporated therein (1) a photosensitizer that upon irradiation generates singlet oxygen, and (2). . .

. . . the presence of said analyte; determining whether said sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties such that upon activation of said photosensitizer property singlet oxygen is generated and activates. . .

14. The method of claim 13, wherein said single **composition** is a solid matrix or a particle having incorporated therein a photosensitizer that upon irradiation generates singlet oxygen and a. .

. . . of containing said analyte, (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both photosensitizer and chemiluminescent properties such that upon activation of said photosensitizer property singlet oxygen is generated and activates. . .

20. The method of claim 19, wherein said single **composition** is a solid matrix or a particle having incorporated therein a photosensitizer that upon irradiation generates singlet oxygen and a. .

30. A **composition** comprising a solid matrix having incorporated therein a photosensitizer that upon activation generates singlet oxygen and a chemiluminescent compound activatable. . .

31. The **composition** of claim 30 wherein said photosensitizer is bound to said chemiluminescent compound.

32. The **composition** of claim 30 wherein at least one of said photosensitizer and said chemiluminescent compound is covalently linked to said matrix.

. . .

33. The **composition** of claim 30 comprising a plurality of distinct chemiluminescent compounds.

34. The **composition** of claim 33 wherein said distinct chemiluminescent compounds differ by differing rates of decay of emission following activation by singlet. . .

35. The **composition** of claim 30 wherein said photosensitizer and said chemiluminescent compound are covalently linked to said matrix.

36. The **composition** of claim 30 which comprises an activator that enhances the decay of activated chemiluminescent compound.

37. The **composition** of claim 30 comprising a member of a specific binding pair (sbp) bound thereto.

38. The **composition** of claim 37 wherein said sbp member is selected from the group consisting of ligands, receptors, polynucleotides and polynucleotide binding. . .

39. The **composition** of claim 30 wherein said photosensitizer is a dye selected from the group consisting of methylene blue, rose bengal, porphyrin,. . .

40. The **composition** of claim 30 wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .

41. The **composition** of claim 30 wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-methyl acridans, enol ethers and enamines.

. . .

42. The **composition** of claim 30 wherein said solid matrix is a particle having as average diameter of about 20 nanometers to 20. . .

43. A **composition** comprising a particle having incorporated therein a photosensitizer that generates singlet oxygen and a chemiluminescent compound activatable by the singlet. . .

44. The **composition** of claim 43 wherein said molecule is a member of a specific binding pair.

45. The **composition** of claim 43 wherein said photosensitizer is covalently bound to said chemiluminescent compound.

46. The **composition** of claim 44 wherein said sbp member is selected from the group consisting of ligands, receptors, polynucleotides and polynucleotide binding. . .

47. The **composition** of claim 43 wherein said photosensitizer is a dye selected from the group consisting of methylene blue, rose bengal, porphyrins,. . .

48. The **composition** of claim 43 wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .

49. The **composition** of claim 43 wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-methyl acridans, enol ethers and enamines.

. . .

50. The **composition** of claim 43 wherein said photosensitizer and said chemiluminescent compound are dissolved in said particle.

51. The **composition** of claim 43 comprising a plurality of distinct chemiluminescent compounds.

52. The **composition** of claim 51 wherein said distinct chemiluminescent compounds differ by differing rates of decay after activation by singlet oxygen.

53. The **composition** of claim 43 which comprises an activator that enhances the decay of activated chemiluminescent compounds.

54. A **composition** comprising fluid particles selected from the group consisting of oil droplets, liposomes and emulsions having incorporated therein a photosensitizer that. . .
55. The **composition** of claim 54 wherein said photosensitizer is bound to said chemiluminescent compound.

56. The **composition** of claim 54 wherein at least one of said photosensitizer and said chemiluminescent compound is covalently linked to said matrix.
. . .
57. The **composition** of claim 54 comprising a plurality of distinct chemiluminescent compounds.

58. The **composition** of claim 57 wherein said distinct chemiluminescent compounds differ by differing rates of decay of emission following activation by singlet. . .
59. The **composition** of claim 54 wherein said photosensitizer and said chemiluminescent compound are covalently linked to molecules comprising said fluid particles.

60. The **composition** of claim 54 which comprises an activator that enhances the decay of activated chemiluminescent compound.

61. The **composition** of claim 54 comprising a member of a specific binding pair (sbp) bound thereto.

62. The **composition** of claim 61 wherein said sbp member is selected from the group consisting of ligands, receptors, polynucleotides and polynucleotide binding. . .
63. The **composition** of claim 54 wherein said photosensitizer is a dye selected from the group consisting of methylene blue, rose bengal, porphyrin,. . .
64. The **composition** of claim 54 wherein said chemiluminescent compound contains an olefin group and one or more electron donating substituents in conjugation. . .
65. The **composition** of claim 54 wherein said chemiluminescent compound is selected from the group consisting of 9-alkylidene-N-methyl acridans, enol ethers and enamines.
. . .
66. A kit comprising: (a) the **composition** of claim 36 and (b) a member of a specific binding pair.

67. A kit comprising: (a) the **composition** of claim 43 and (b) a member of a specific binding pair.

68. A kit comprising: (a) the **composition** of claim 55 and (b) a member of a specific binding pair.

. . . for determining a leak in a fluidic system, said method comprising:

introducing into a fluid in the fluidic system a **composition** comprising a non-particulate solid matrix or a particulate matrix, said matrix having incorporated therein (1) a photosensitizer that upon irradiation. . .

71. A method for determining wear in a mechanical pad comprising: incorporating into the mechanical part a **composition** comprising a non-particulate solid matrix or a particulate matrix, said matrix having incorporated therein (1) a photosensitizer that upon irradiation. . .

73. A method for detecting the emission of light comprising: irradiating a **composition** comprising a non-particulate solid matrix or a particulate matrix, said matrix having incorporated therein (1) a photosensitizer that upon irradiation. . .

L14 ANSWER 10 OF 45 USPATFULL

ACCESSION NUMBER:	97:104285 USPATFULL
TITLE:	Method of stabilizing enzyme conjugates
INVENTOR(S):	Skold, Carl N., Mountain View, CA, United States Henson, Margaret, Mountain View, CA, United States Houts, Thomas Michael, Mountain View, CA, United States Gibbons, Ian, Portola Valley, CA, United States
PATENT ASSIGNEE(S):	Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5686253		19971111
APPLICATION INFO.:	US 1995-450744		19950525 (8)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1990-616115, filed on 20 Nov 1990, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Saunders, David
LEGAL REPRESENTATIVE:	Leitereg, Theodore J.
NUMBER OF CLAIMS:	44
EXEMPLARY CLAIM:	1
LINE COUNT:	1905

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM In developing an enzyme conjugate for use as an assay reagent stability is an important consideration. An enzyme conjugate **composition** used in an assay is usually prepared well in advance of the time the assay procedure is performed. Storage of. . . be subjected to wide temperature variations and other conditions which promote the loss of enzyme activity. Accordingly, an enzyme conjugate **composition** which exhibits substantially improved stability characteristics by comparison with known compositions is a useful improvement in the assay field.

SUMM Another aspect of the invention concerns a **composition** comprising an immune complex comprised of (1) a conjugate of an enzyme and a member of a specific binding pair and (2) an antibody for the enzyme where the antibody does not substantially inhibit the enzyme. The **composition** can further include a second member of a specific binding pair where the second member is usually capable of binding. . .

SUMM Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzoyl ecgonine, their derivatives and metabolites, ergot alkaloids, which include the diethylamide of lysergic
acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, and their metabolites.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . Spore-forming Bacilli
Phialophora jeanselmei
Bacillus anthracis
Microsporum gypseum
Bacillus subtilis Trichophyton mentagrophytes
Bacillus megaterium
Keratinomyces ajelloi
Bacillus cereus Microsporum canis
Anaerobic Spore-forming Bacilli
Trichophyton rubrum
Clostridium **botulinum**
Microsporum adouini
Clostridium tetani
Viruses
Clostridium perfringens
Adenoviruses
Clostridium novyi Herpes Viruses
Clostridium septicum
Herpes simplex
Clostridium histolyticum
Varicella (Chicken pox)
Clostridium tertium
Herpes Zoster (Shinglee)
Clostridium. . .

SUMM Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

SUMM Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

SUMM In accordance with the present invention, a **composition** is employed in place of enzyme labeled sbp member. The **composition** comprises enzyme labeled sbp member and antibody for the enzyme that does not substantially inhibit the activity of the enzyme. . .

SUMM . . . and a second sbp member complementary to the analyte can be bound to the support. In any such instance, a **composition** in accordance with the present invention can be substituted for the enzyme conjugate reagent. Exemplary of heterogeneous immunoassays are the. . .

SUMM . . . one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises as one reagent a **composition** in accordance with the invention. As mentioned

above, for homogeneous immunoassays the preferred enzymes of the enzyme conjugate are dehydrogenases,. . .

DETD . . . 100 .mu.g (12 "high dose" mice) or 10 .mu.g (12 "low dose" mice) of G6PDH. The immunogen was a 50:50 **mixture** of United States Biochemicals (USB) Cat. No. 16190 and Cooper Cat. No. 9869 G6PDH in CFA, boosted once with 100. . .

DETD Fusions were initially screened by a Forward ELISA using a 50:50 **mixture** of USB and Cooper G6PDH as a plate coat. This initial screen was followed by an Enzyme Thermal Protection Assay. . .

DETD (1) Costar EIA plates were coated with 50 .mu.L/well of a 50 .mu.g/mL equal **mixture** of Cooper and USB G6PDH in PBS, pH 7.2, for 1-2 hrs. at 37.degree. C. The plates were blocked for. . .

DETD . . . quinidine-G6PDH conjugate were prepared as follows: Quinidine-G6PDH (.about.0.2 mg/ml) was mixed with a molar excess of antibody (.about.3 mg/ml). The **mixture** was incubated at 45.degree. for 10' before measuring activity. A control sample was kept cold. Heating by itself at 45.degree.. . .

DETD (e) Using a Pipetman, 300 .mu.L from the step a cup were added to the assay cup, and the **mixture** was read on the Stasar.

DETD . . . U.S. Pat. No. 3,817,837 (1974). An antibody capable of recognizing cyclosporin A was prepared by routine hybridoma techniques using a **mixture** of cyclosporin A conjugated, through a glycylglycine extended para-carboxybenzyl linking group, at the alanine nitrogen atoms of cyclosporin A amino. . .

DETD . . . methanol lysed the cells, solubilizes the cyclosporin A, and precipitates most of the blood proteins. After a one-minute incubation, the **mixture** was centrifuged. The supernatant was diluted 1 to 3 with pretreatment diluent. On the analyzer, 36 .mu.L of the resulting.

. .

CLM What is claimed is:

28. A **composition** comprising (1) a conjugate of an enzyme and a member of a specific binding pair (sbp) having a molecular weight. . . the sbp member of said conjugate to bind to its complementary sbp member, wherein said antibody is present in said **composition** in a molar amount that is 5-fold or greater than the molar amount of said conjugate, said amount being sufficient. . .

29. The **composition** of claim 28 wherein said enzyme is a dehydrogenase.

30. The **composition** of claim 28 wherein said enzyme is a glucose-6-phosphate dehydrogenase.

31. The **composition** of claim 28 wherein said enzyme is malate dehydrogenase.

32. The **composition** of claim 28 wherein said enzyme is horseradish peroxidase.

33. The **composition** of claim 28 wherein said enzyme is glucose oxidase.

34. The **composition** of claim 28 wherein said member is a hapten.

35. The **composition** of claim 28 wherein said antibody for said enzyme is a monoclonal antibody.

36. A kit comprising in packaged combination (a) **composition** comprised of (1) a conjugate of an enzyme and a member of a specific

binding pair (sbp) having a molecular. . . inhibit the ability of said member to bind to its complementary sbp member, wherein said antibody is present in said **composition** in a molar amount that is 5-fold or greater than the molar amount of said conjugate, said amount being sufficient. . .

L14 ANSWER 11 OF 45 USPATFULL
ACCESSION NUMBER: 97:88865 USPATFULL
TITLE: Methods of use for and kits containing chemiluminescent compounds
INVENTOR(S): Singh, Sharat, San Jose, CA, United States
Singh, Rajendra, Mountain View, CA, United States
Meneghini, Frank, Keene, NH, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5672478		19970930
APPLICATION INFO.:	US 1996-661846		19960611 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-373678, filed on 17 Jan 1995, now patented, Pat. No. US 5545834 which is a continuation of Ser. No. US 1992-916453, filed on 20 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Marschel, Ardin H.
ASSISTANT EXAMINER: Riley, Jezia
LEGAL REPRESENTATIVE: Leitereg, Theodore J.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1892
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .
DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
DETD . . . group
Hemophilus influenzae
H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pastourella tulareusis
Brucellae
Brucalla melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Baclllus subtilis

Bacillus megaterium
Bacillus cerous
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septic
Clostridium histolyticum
Clostridium tertium
Clostridium bifermontans
Clostrldium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycotes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polynucleotide: a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD . . . context of the present invention, a ligand conjugated to a chemiluminescent label of this invention, is a ligand-label conjugate. A **composition** which is described as comprising subunit A conjugated to subunit B is a **composition** wherein subunit A is bound to subunit B.

DETD One embodiment of the present invention pertains to a chemiluminescent **composition** comprising a chemiluminescent compound of this invention in a pH 6-10 aqueous solution containing hydrogen peroxide or a means for. . . a hapten or an antibody, in the manner described above. Compound (I) is particularly suited for use in such a **composition**. If peroxide is to be detected, it will usually be desirable to have a relatively high concentration of the

chemiluminescent. . .

DETD Another embodiment of the present invention is a light emitting chemical **composition** comprised of hydrogen peroxide and a chemiluminescent compound of this invention, for example, Compound (II).

It is usually desirable to. . .

DETD . . . produce hydrogen peroxide as a function of the presence of the analyte, and (3) detecting the luminescence produced by the **mixture**; where the components may be added in any convenient order.

DETD . . . compound can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD . . . a chemiluminescent compound of this invention in a tube coated with antibodies to the HBsAg antigen. After incubation of the **mixture** for one hour, the tubes are washed and hydrogen peroxide is added. The emitted light intensity is related to the. . .

DETD One such kit comprises in packaged combination (1) a **composition** comprising a chemiluminescent compound of this invention, for example Compound (I), having bound thereto a specific binding pair member and. . . of hydrogen peroxide or an analyte that modulates the formation of hydrogen peroxide, and comprises in packaged combination (1) a **composition** comprising the compound A--L--Q described herein and (2) any ancillary reagents required to produce hydrogen peroxide from said analyte when. . .

DETD The reaction **mixture** was heated to 70.degree. C. with gentle stirring for 24 hours under argon. The solvent was evaporated under vacuum to. . .

DETD . . . DMF, were added the carboxylate (3) (274 mg, 1.0 mmol) and carbonyl diimidazole (CDI) (225 mg, 1.5 mmol). The reaction **mixture** was stirred at room temperature for 16 hours. At this point, an aliquot of reaction **mixture** was found to be highly chemiluminescent when perborate (pH 9.5) was added. 1,2,4-Trihydroxybenzene (504 mg, 4.0 mmol) in 3 mL of acetonitrile was added to the above reaction **mixture**. The reaction was allowed to sit under argon for 12 hours. ##STR22## The solvent was evaporated under vacuum to obtain. . .

DETD . . . g, 48.1 mmol) in CH.sub.2 Cl.sub.2 (100 mL) was treated with methane sulfonyl chloride (3.6 mL, 46.5 mmol) and the **mixture** stirred until TLC indicated absence of starting material. The **mixture** was concentrated, adsorbed on alumina and chromatographed with a gradient of CH.sub.3 OH (0-5%) in CH.sub.2 Cl.sub.2 as the eluant.. . .

DETD . . . of (CH.sub.3 CH.sub.2).sub.3 N. ##STR24## The initial yellow solution, which rapidly turned almost colorless, was stirred for 14 hours. The **mixture** was concentrated and purified by preparative TLC (silica, CH.sub.2 Cl.sub.2 eluant) to yield 52 mg (60%) of the Compound (IIIa). . .

DETD . . . a vacuum oven at 50.degree. C. The .sup.1 H-NMR showed the crude to be a 4:1 (compound (8): compound (9)) **mixture** of isomers. Crystallization from boiling water afforded 4.10 g (56%) of the sulfonanilide (8) as tan flakes.

DETD . . . the sulfonanilide (8) (120 mg, 0.45 mmol). The initial yellow solution gradually turned almost clear, indicating adduct formation. The reaction **mixture** was concentrated after TLC indicated absence

of starting materials. ##STR26## The concentrate was passed through silica (100 g, 10% CH.sub.3 CN in CH.sub.2 Cl.sub.2) and the higher R.sub.f (0.60-0.40) material, which was a **mixture** of two compounds, was collected. The **mixture** (260 mg) was dissolved in anhydrous DMF (20 mL) and treated with NaH (100 mg), batch-wise, allowing the initial effervescence to subside before subsequent additions. After 3 hours, the reaction **mixture** was quenched with 10% aqueous NH.sub.4 Cl (2 mL) and extracted with CH.sub.2 Cl.sub.2
(3.times.50 mL). The aqueous portion was. . .

DETD . . . to 0.degree. C. Methane sulfonyl chloride (1.8 mL), 19.0 mmol) was slowly added over a period of ten minutes. The **mixture** was stirred for 6 hours and allowed to attain room temperature over this period. The pyridine was distilled off after. . .

CLM What is claimed is:
33. A kit comprising in packaged combination (1) a **composition** comprising the compound of claim 1 having bound thereto a specific binding pair (sbp) member and (2) hydrogen peroxide or. . . . . detection of hydrogen peroxide or an analyte that modulates the formation of hydrogen peroxide, comprising in packaged combination (1) a
composition comprising the label reagent of claim 6 and (2) any ancillary reagents required to produce hydrogen peroxide from said analyte. . .

L14 ANSWER 12 OF 45 USPATFULL

ACCESSION NUMBER:	97:49519 USPATFULL
TITLE:	Heterogeneous assay using a pendulous drop
INVENTOR(S):	Meltzer, Robert J., Kirkland, WA, United States
PATENT ASSIGNEE(S):	Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5637467		19970610
APPLICATION INFO.:	US 1995-412636		19950329 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1992-960032, filed on 13 Oct 1992, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Housel, James C.		
ASSISTANT EXAMINER:	King, Theresa		
LEGAL REPRESENTATIVE:	Precivale, Shelley G., Kaku, Janet K., Clarke, Pauline Ann		
NUMBER OF CLAIMS:	55		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	3 Drawing Figure(s); 2 Drawing Page(s)		
LINE COUNT:	1529		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .

DETD The microorganisms that are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD Clostridium **botulinum**

DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which

include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic
acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs, which include
methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polynucleotide: a compound or **composition** that is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

L14 ANSWER 13 OF 45 USPATFULL

ACCESSION NUMBER:	97:29389 USPATFULL
TITLE:	Method of calibration with photoactivatable chemiluminescent matrices
INVENTOR(S):	Pease, John S., Los Altos, CA, United States Kirakossian, Hrair, San Jose, CA, United States Wagner, Daniel B., Sunnyvale, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5618732		19970408
APPLICATION INFO.:	US 1995-434617		19950504 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1992-923069, filed on 31 Jul 1992		

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Snay, Jeffrey
LEGAL REPRESENTATIVE:	Leitereg, Theodore J.
NUMBER OF CLAIMS:	3
EXEMPLARY CLAIM:	1
LINE COUNT:	2936

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . presence of the analyte and determining whether the sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties. Upon activation of the photosensitizer property singlet oxygen is generated and activates the chemiluminescent. . .

SUMM U.S. Pat. No. 4,311,712 (Evans, et al.) discloses a process for preparing a freeze dried liposome **mixture**.

SUMM . . . in a fluidic system, (c) wear in a mechanical part or (d) emission of light. The method comprises irradiating a **composition** arising from or subject to the condition. The **composition** comprises a non-particulate solid matrix or a particulate matrix having incorporated therein (a) a photosensitizer capable upon irradiation of generating. . .

SUMM . . . aspect of the present invention concerns a method for generating delayed luminescence. The method comprises the step of irradiating a **composition** comprising a non-particulate, solid matrix or particulate solid or fluid matrix having incorporated therein (1) a photosensitizer capable upon irradiation. . .

SUMM . . . presence of the analyte and determining whether the sbp member complex has formed by employing as a label a single **composition** having both chemiluminescent and photosensitizer properties such that upon activation of the photosensitizer property singlet oxygen is generated and activates. . .

SUMM . . . of containing said analyte, (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both photosensitizer and chemiluminescent properties such that upon activation of the photosensitizer property singlet oxygen is generated and activates. . .

SUMM Another embodiment of the invention is a **composition** comprising a non-particulate solid matrix or particulate solid or fluid having incorporated therein a photosensitizer capable upon activation of generating. . .

SUMM Another **composition** in accordance with the invention comprises a particle, either solid or fluid, having incorporated therein a photosensitizer capable of generating. . .

SUMM Another embodiment of the invention is a **composition** comprising fluid particles selected from the group consisting of oil droplets, liposomes and emulsions having incorporated therein a photosensitizer capable. . .

SUMM Another embodiment of the present invention is a method for calibrating light intensity emitted by a luminescent **composition**, The method comprises the steps of (a) combining in a medium a luminescent **composition** capable of emitting light upon irradiation and one of the above compositions of the invention, wherein one of the compositions. . . for light emission substantially greater than the decay time for the other, (b) irradiating the medium to activate the luminescent **composition** and the **composition** of the invention, (c) measuring the intensity of light emitted during the decay of the activated **composition** having the shorter decay time, (d) measuring the intensity of light emitted after the measuring of step (c) and after at least partial decay of the activated **composition** having the shorter decay time, and (e) comparing the intensity of the light emitted during the decay of the activated **composition** having the shorter decay time with the intensity of light emitted in step (d) to provide for internal calibration. Steps b and c may be repeated one or more times prior to step d. In one embodiment the activated **composition** of **composition** of the invention has the shorter decay time. Another embodiment of the present invention is a kit comprising one of. . .

DETD . . . lifetime of the luminescent decay is determined by a number of factors including the structure of the chemiluminescent compound, the **composition** of the solid material or the particle, the temperature and the presence of activators that enhance the rate of decomposition. . .

DETD . . . gas. Application of tracers to detect leaks is well-known in the art. In general, about 10.sup.-14 -10.sup.-2 % of a **composition** of the invention is dispersed into the liquid or gas. Next, the fluid is irradiated with light to activate the. . .

DETD . . . reaction of singlet oxygen with the chemiluminescent compound to be sufficiently stable so that luminescence will not occur until the

composition is heated. Preferably, for these applications the **composition** is in the form of a film. The compositions may also be used to calibrate light sources and photometric devices.. . .

DETD . . . where they can be used as a label or as part of a labeled reagent. For the most part the **composition** will have a member of a specific binding pair (sbp) bound to its surface. The sbp member may be capable. . .

DETD Where the molecule to be detected involves a cell, the cell can be labeled with a particulate **composition** of the invention. For example, the **composition** of the invention can include an sbp member complementary to an sbp member on the surface of the cell. The. . .

DETD The present compositions can be utilized for internal calibration in luminescent assays. By including particles of the **composition** in an assay medium in which luminescence is produced by irradiating the medium, the **composition** produces an emission that can be detectably different from that produced in the assay. This difference can be the result. . .

DETD . . . a fluorescence immunoassay the fluorescence intensity is measured first. Irradiation of the medium is discontinued and luminescence emanating from the **composition** of the invention is measured to provide an accurate internal reference of light intensity, detector sensitivity and sample interference. The. . . the measurement. Following the final cycle, the intensity of light which will now be emanating primarily from the present particulate **composition** can be independently measured because the decay times for the present particulate compositions are much longer. The residual light intensity. . . can be ratioed against the residual intensity of the present particulate compositions to provide for internal calibration. Conversely the present **composition** decay times could be shorter than the '490 **composition** decay times and the same procedure could be used for calibration except that the rapidly decaying light intensity would serve. . .

DETD An assay for an analyte may be accomplished by separating a particulate **composition** of the invention used as a label, to which has become bound an analyte or an sbp member whose presence is indicative of the presence of an analyte, from unbound **composition**. Either the separated bound or unbound fraction is treated to activate the photosensitizer, usually by irradiation with light, and the. . .

DETD Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

DETD . . . Spore-forming Bacilli

Phialophora jeanselmei

Bacillus anthracis Microsporum gypseum

Bacillus subtilis Trichophyton mentagrophytes

Bacillus megaterium

Keratinomyces ajelloi

Bacillus cereus Microsporum canis

Anaerobic Spore-forming Bacilli

Trichophyton rubrum

Clostridium **botulinum**

Microsporum adouini

Clostridium tetani Viruses

Clostridium perfringens

Adenoviruses

Clostridium novyi Herpes Viruses

Clostridium septicum

Herpes simplex
Clostridium histolyticum
Varicella (Chicken pox)
Clostridium tertium
Herpes Zoster (Shingles)
Clostridium. . .
DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeins, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic
acid; steroid alkaloids; iminazoyl alkaloids;. . .
DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and metabolites of the above.
DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.
DETD Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .
DETD Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .
DETD . . . the most part, when a linking group is bound to the photosensitizer, the photochemically activatable chemiluminescent compound or a particulate **composition** of the invention will have a non-oxocarbonyl group including nitrogen and sulfur analogs, a phosphate group, an amino group, alkylating. . .
DETD . . . the above functionalities can also be utilized as attaching groups, which permit attachment of an sbp member to a particulate **composition** comprised of the photosensitizer and chemiluminescent compound.
DETD . . . chemical reagents is required to activate the present compositions and the photosensitizer and the chemiluminescent compound are found within one **composition**.
DETD . . . case these compounds will preferably be hydrophobic to reduce their ability to dissociate from the particle. In general the particle **composition** is chosen so as to favor association of the photosensitizer and the chemiluminescent compound with the particle.
DETD . . . surfactant is present in from about 0.1 to 5, more usually from
about 0.1 to 2 weight percent of the **mixture** and subjecting the **mixture** in an aqueous medium to agitation, such as sonication or vortexing. Illustrative lipophilic compounds include hydrocarbon oils, halocarbons including fluorocarbons,. . .
DETD . . . frequently comprised of phospholipids. Phospholipids employed in preparing particles utilizable in the present invention can be any phospholipid or phospholipid **mixture** found in natural membranes including lecithin, or synthetic glyceryl phosphate diesters of saturated or unsaturated 12-carbon or 24-carbon linear fatty. . .

DETD . . . a variety of methods, including a method described by Olsen, et
al., Biochemica et Biophysica Acta, 557(9), 1979. Briefly, a

mixture of lipids containing the appropriate compound(s) in an organic solvent such as chloroform is dried to a thin film on. . .

DETD . . . CC can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD . . . particles in accordance with the present invention. Polystyrene particles (175 nm) are prepared by heating in the presence of a **mixture** of both photosensitizer and CC. The medium employed is a **mixture** of water, ethylene glycol, and benzyl alcohol in the approximate ratio of 1:8:1 by volume. This **mixture** provides a balance of both aqueous and organic properties. A water-like solvent is preferred to maintain the colloidal stability of. . .

DETD . . . CC are separately prepared as solutions (5 mM) in benzyl alcohol. Aliquots in varying ratios are then added to a **mixture** of ethylene glycol, benzyl alcohol 9:1 by volume and the **mixture** heated to 100.degree. to 110.degree.. Appropriate aliquots of the particles, into which the photosensitizer and the CC are to be incorporated, are then added to the hot **mixture** while stirring vigorously. Heating is continued briefly and then the **mixture** is cooled and diluted with ethanol. Excess dye and solvent **mixture** are removed by repeated centrifugation. Finally, the washed particles are resuspended in a convenient volume of water (generally 100 mg. . .

DETD . . . containing an analyte and (2) a label reagent comprising a first specific binding pair (sbp) member associated with a single **composition** having both a photosensitizer and a CC. Conditions are chosen such that an sbp member complex is formed in relation. . .

DETD Another factor that allows for control of the time to luminescence is the **composition** or the particle. In general, when the particle is composed of a non-polar material in which the CC is dissolved. . .

DETD . . . formed in relation to the presence of the analyte and determining whether the sbp member complex has formed. A particulate **composition** of the invention is employed as a label to assist in the determination. An sbp member complex involving the label reagent is formed in relation to the presence of analyte in the medium. The **composition** is then irradiated with light and light energy from the chemiluminescent compound is measured such as, for example, by visual. . .

DETD Another aspect of the present invention is a **composition** comprising a solid matrix having incorporated therein a photosensitizer capable upon activation of generating singlet oxygen and a chemiluminescent compound. . . compound can be covalently linked to the matrix or can be associated with the matrix with no covalent bounds. The **composition** can comprise one or a plurality of distinct chemiluminescent compounds and one or a plurality of distinct photosensitizers and can. . . energy from the chemiluminescent compound. The distinct chemiluminescent compounds may differ by differing rates of activation by singlet oxygen. The **composition** may also comprise an activator that may or may not be fluorescent and that enhances the decay of an activated chemiluminescent compound. The **composition** can further comprise a member of a specific binding pair (sbp) bound thereto wherein the **composition** is usually particulate.

DETD Another aspect of the present invention is a **composition** comprising a particle having incorporated therein a photosensitizer capable of generating singlet oxygen and a chemiluminescent compound capable of being. . .

DETD . . . above. The amount of Reagent 1 is sufficient to provide a concentration of antibody of about 10.sup.-8 molar. The reaction **mixture** is then added to the microtiter plate well (Reagent 2) and incubated for a period of one hour at 25.degree. C. The reaction **mixture** is then removed from the well and the plate is washed with a buffered aqueous medium at pH 8.0 and. . . TSH to determine the concentration of TSH in the unknown. Alternatively, following incubation and removal from the well, the reaction **mixture** containing unbound latex particles is similarly irradiated, and the amount of light emitted from the system is measured and compared. . .

DETD . . . containing an anti .alpha.-chain antibody labeled with fluorescein and an anti hCG .beta.-chain antibody labeled with biotin. After incubating the **mixture** for 10 minutes, there is added to the **mixture** 200 .mu.L of a suspension containing 2 .mu.g of each of the above beads and 1 .mu.g of 180 nm. . . the present invention) containing both chlorophyll and 1-phenyl-2-p-dimethylaminophenyl-5,6-dihydro-1,4-dioxene, a chemiluminescent acceptor that decays with a 2 minute half life. The **mixture** is incubated for 10 minutes and then irradiated for one second with a tungsten-halogen lamp equipped with a 650 nm. . .

DETD . . . be combined in one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises a **composition** comprising a suspendible particle having associated therewith a chemiluminescent compound and a photosensitizer, the particle having an sbp member bound. . .

DETD . . . (nC.sub.10 PC) (particle preparations A, B, C, D, respectively) and 10 ul C.sub.18 benzal acridan were mixed together and the **mixture** was heated to 100.degree. to 110.degree. C. for 1 min. Then, 0.1 ml of 0.716 .mu. CML was added to the **mixture**, which was heated for 5 min at 100.degree. to 110.degree.. The **mixture** was allowed to cool to room temperature. Equal volumes of ethanol were added and the **mixture** was centrifuged at 15K for 30 min. The centrifugate was decanted and the particles were combined with 2 ml of. . .

DETD . . . of nC.sub.10 PC (10, 25, or 50.mu.). Heating was continued for 10 min. An effort was made to keep the **mixture** just slightly below the boiling point of the water, but occasionally boiling was observed.

DETD . . . 10 .mu.g/ml in 0.1M Tris 0.3M NaCl, 25 mM EDTA, 1 mg/ml BSA pH 8.2. 0.1 ml of this diluted **mixture** was illuminated with a halogen lamp fitted with a 610 nm long pass filter for 60 sec. The first 20. . .

DETD . . . Chemical Co.) (3.22 g, 28 mmole) was added as a solid to the DMF solution and allowed to dissolve. The **mixture** was then cooled in an ice bath. Dicyclohexylcarbodiimide (Aldrich Chemical Co.) (5.8g, 28 mmole) was dissolved in dry DMF (10 ml) and added all at once to the cold DMF solution. The **mixture** was stirred at ice bath temperature for 30 min. and then allowed to come to room temperature. The course of. . .

DETD 4,9-Dioxa-1,12-dodecane diamine (25.5g, 125 mmole) was diluted with dry DMF (10 ml). The fluorescein NHS ester reaction **mixture** was cooled in ice under an argon atmosphere and the diamine solution added dropwise over a period of 5 minutes.. . . The course of the reaction was followed by tlc using the above system. When the reaction was judged complete, the **mixture** was diluted with water (100 ml) and cooled in ice to precipitate dicyclohexylurea, which was removed by

filtration.

DETD . . . solution. Diglycolic anhydride (Aldrich Chemical Co.) (101 mg, 0.87 mmole) was dissolved in 1 ml DMF and added to the **mixture** . An additional 25 mg of diglycolic anhydride was added to force the reaction to completion as judged by silica gel. . .

DETD . . . prepared as described above in Part C) with 12 mg of dicyclohexylcarbodiimide (DCC) (in 100.mu. of anhydrous DMF). The reaction **mixture** was stirred gently at room temperature for 5 hours in a tightly closed vial. Then, the reaction **mixture** was filtered through glass wool to remove cyclohexylurea (side product of this reaction). The filtered reaction **mixture** was extracted with 2 ml of hexane (to remove unreacted DCC). The formation of F-LC.sub.19 -NHS was confirmed by TLC. . .

DETD . . . with 20.mu. of anhydrous DMF containing F-LC.sub.19 -NHS (IgG: F-LC.sub.19 -NHS.tbd.1:20) at room temperature for 2 hrs. Then, the reaction **mixture** was purified by Sephadex G-25 (1.5.times.20 cm) column equilibrated in 0.02 M NaPi, 0.15 M NaCl, pH7.4. The hapten number. . .

DETD . . . small aliquot used for the reaction) were mixed together and incubated for three hours at 4.degree. C. In the reaction **mixture**, the molar ratio of the reactants was Ab.sub.1 :Biotin-LC.sub.7 -NHS=1:25. The uncoupled biotin was removed by Sephadex.RTM. G-25 column. The. . .

DETD . . . of 0.02 M Borax (Sigma Chemical Company), 0.08 M NaCl, 2 mg/mL 3G1 IgG(Ab.sub.F), and 8 mg/mL BSA/pH 8.9. The **mixture** was gently mixed (no stirring) overnight at 4.degree. C. The remaining reactive groups on the beads (if any) were blocked. . .

DETD . . . and 1 .mu.g/mL Ab.sub.2 -fluorescein (9G3) in assay buffer (0.05 M NaPi, 0.15 M NaCl, 4 mg/mL BSA/pH 7.6). This **mixture** was incubated at room temperature for 1 hour. To this **mixture** 100 .mu.L of 1M Na.sub.3 Citrate/pH 7.17 was added, followed by 100 .mu.L of 1.0 mg/mL Ab.sub.F -bead in assay. . . from the unbound fraction by 0.5 cm glass beads coated with avidin (one glass bead per tube used). The assay **mixture** was incubated with the glass beads for 2.5 hours at room temperature (shaking in dark). After incubation, each glass bead. . .

CLM What is claimed is:

1. A method for calibrating light intensity emitted by a luminescent **composition**, said method comprising the steps of: (a) combining in a medium a luminescent **composition** capable of emitting light upon irradiation and a **composition** comprising a solid matrix having incorporated therein a photosensitizer capable upon activation of generating singlet oxygen and a chemiluminescent compound.

. . for light emission substantially greater than the decay time for the other, (b) irradiating said medium to activate said luminescent **composition** and said **composition**, (c) measuring the intensity of light emitted during the decay of the activated **composition** having the shorter decay time, (d) measuring the intensity of light emitted after said measuring of step (c) and after at least partial decay of the activated **composition** having the shorter decay time, and (e) comparing the intensity of the light emitted during the decay of the activated **composition** having the shorter decay time with the intensity of light emitted in step (d) to provide for internal calibration.

3. The method of claim 1 wherein said activated **composition** comprising said solid material has the shorter decay time.

L14 ANSWER 14 OF 45 USPATFULL
ACCESSION NUMBER: 96:73076 USPATFULL
TITLE: Chemiluminescent compounds and methods of use
INVENTOR(S): Singh, Sharat, San Jose, CA, United States
Singh, Rajendra, Mountain View, CA, United States
Meneghini, Frank, Keene, NH, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Behringwerke AG, Marburg, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5545834		19960813
APPLICATION INFO.:	US 1995-373678		19950117 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-916453, filed on 20 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Datlow, Philip I.
LEGAL REPRESENTATIVE: Precivale, Shelley G., Leitereg, Theodore J.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1932
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Analyte: the compound or **composition** to be detected. The analyte can be a member of a specific binding pair ("sbp") and may be a ligand,. . .

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD Clostridium **botulinum**

DETD . . . Included among drugs of interest are the alkaloids: morphine alkaloids, which include morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and derivatives and metabolites of the above.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD Receptor ("antiligand"): any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polynucleotide: a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

DETD . . . context of the present invention, a ligand conjugated to a chemiluminescent label of this invention, is a ligand-label conjugate.

A

composition which is described as comprising subunit A conjugated to subunit B is a **composition** wherein subunit A is bound to subunit B.

DETD One embodiment of the present invention pertains to a chemiluminescent **composition** comprising a chemiluminescent compound of this invention in a pH 6-10 aqueous solution containing hydrogen peroxide or a means for. . . a hapten or an antibody, in the manner described above. Compound (I) is particularly suited for use in such a **composition**. If peroxide is to be detected, it will usually be desirable to have a relatively high concentration of the chemiluminescent. . .

DETD Another embodiment of the present invention is a light emitting chemical **composition** comprised of hydrogen peroxide and a chemiluminescent compound of this invention, for example, Compound (II).

It is usually desirable to. . .

DETD . . . produce hydrogen peroxide as a function of the presence of the analyte, and (3) detecting the luminescence produced by the **mixture**; where the components may be added in any convenient order.

DETD . . . compound can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

DETD . . . a chemiluminescent compound of this invention in a tube coated with antibodies to the HBsAg antigen. After incubation of the **mixture** for one hour, the tubes are washed and hydrogen peroxide is added. The emitted light intensity is related to the. . .

DETD One such kit comprises in packaged combination (1) a **composition** comprising a chemiluminescent compound of this invention, for example Compound (I), having bound thereto a specific binding pair member and. . . of hydrogen peroxide or an analyte that modulates the formation of hydrogen peroxide, and comprises in packaged combination (1) a **composition** comprising the compound A-L-Q described herein and (2) any ancillary reagents required to produce hydrogen peroxide from said analyte when. . .

DETD The reaction **mixture** was heated to 70.degree. C. with gentle stirring for 24 hours under argon. The solvent was evaporated under vacuum to. . .

DETD . . . DMF, were added the carboxylate (3) (274 mg, 1.0 mmol) and carbonyl diimidazole (CDI) (225 mg, 1.5 mmol). The reaction **mixture** was stirred at room temperature for 16 hours. At this point, an aliquot of reaction **mixture** was found to be highly chemiluminescent when perborate (pH 9.5) was added. 1,2,4-Trihydroxybenzene (504 mg, 4.0 mmol) in 3 mL of acetonitrile was added to the above reaction **mixture**. The reaction was allowed to sit under argon for 12 hours. ##STR23## The solvent was evaporated under vacuum to obtain. . .

DETD . . . g, 48.1 mmol) in CH.sub.2 Cl.sub.2 (100 mL) was treated with methane sulfonyl chloride (3.6 mL, 46.5 mmol) and the **mixture** stirred until TLC indicated absence of starting material. The **mixture** was concentrated, adsorbed on alumina and chromatographed with a gradient of CH.sub.3 OH (0-5%) in CH.sub.2 Cl.sub.2 as the eluant.. . .

DETD . . . of (CH.sub.3 CH.sub.2).sub.3 N. ##STR25## The initial yellow solution, which rapidly turned almost colorless, was stirred for 14 hours. The **mixture** was concentrated and purified by preparative TLC (silica, CH.sub.2 Cl.sub.2 eluant) to yield 52 mg (60%)

of the Compound (IIIa). . .

DETD . . . a vacuum oven at 50.degree. C. The .sup.1 H-NMR showed the crude to be a 4:1 (compound (8): compound (9)) **mixture** of isomers. Crystallization from boiling water afforded 4.10 g (56%) of the sulfonanilide (8) as tan flakes.

DETD . . . the sulfonanilide (8) (120 mg, 0.45 mmol). The initial yellow solution gradually turned almost clear, indicating adduct formation. The reaction **mixture** was concentrated after TLC indicated absence of starting materials. ##STR27## The concentrate was passed through silica (100 g, 10% CH.sub.3 CN in CH.sub.2 Cl.sub.2) and the higher R.sub.f (0.60-0.40) material, which was a **mixture** of two compounds, was collected. The **mixture** (260 mg) was dissolved in anhydrous DMF (20 mL) and treated with NaH (100 mg), batch-wise, allowing the initial effervescence to subside before subsequent additions. After 3 hours, the reaction **mixture** was quenched with 10% aqueous NH.sub.4 Cl (2 mL) and extracted with CH.sub.2 Cl.sub.2 (3.times.50 mL). The aqueous portion was. . .

DETD . . . to 0.degree. C. Methane sulfonyl chloride (1.8 mL), 19.0 mmol) was slowly added over a period of ten minutes. The **mixture** was stirred for 6 hours and allowed to attain room temperature over this period. The pyridine was distilled off after. . .

CLM What is claimed is:

4. A chemiluminescent **composition** comprised of the compound of claim 1 in a pH 6-10 aqueous solution containing hydrogen peroxide.

5. A light emitting chemical **composition** comprising hydrogen peroxide and a compound having the following formula: ##STR34## wherein:

X' is selected from the group consisting of. . .

6. The **composition** of claim 5 wherein said compound is chemiluminescent and wherein said **composition** further comprises a catalyst to enhance chemiluminescence.

9. The **composition** of claim 5 wherein said compound has the formula: ##STR37##

L14 ANSWER 15 OF 45 USPATFULL

ACCESSION NUMBER:	94:73204 USPATFULL
TITLE:	Assay method utilizing photoactivated chemiluminescent label
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Kirakossian, Hrair, San Jose, CA, United States Pease, John S., Los Altos, CA, United States Daniloff, Yuri, Mountain View, CA, United States Wagner, Daniel B., Sunnyvale, CA, United States
PATENT ASSIGNEE(S):	Snytex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5340716		19940823	
APPLICATION INFO.:	US 1991-718490		19910620	(7)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Wax, Robert A.			
ASSISTANT EXAMINER:	Schmickel, David			

LEGAL REPRESENTATIVE: Leitereg, Theodore J.
NUMBER OF CLAIMS: 86
EXEMPLARY CLAIM: 1
LINE COUNT: 2698
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM U.S. Pat. No. 4,311,712 (Evans, et al.) discloses a process for preparing a freeze dried liposome **mixture**.

SUMM Another embodiment of the invention is a **composition** comprising a photochemically activatable chemiluminescent compound bound to an sbp member.

SUMM Another embodiment of the invention is a kit comprising the above **composition**.

SUMM Analyte--the compound or **composition** to be detected. The analyte can be comprised of a member of a specific binding pair (sbp) and may be. . .

SUMM . . . Spore-forming Bacilli
Phialophora jeanselmei
Bacillus anthracis Microsporum gypseum
Bacillus subtilis Trichophyton
mentagrophytes
Bacillus megaterium Keratinomyces ajelloi
Bacillus cereus Microsporum canis
Anaerobic Spore-forming Bacilli
Trichophyton rubrum
Clostridium **botulinum**
Microsporum adouini
Clostridium tetani Viruses
Clostridium perfringens
Adenoviruses
Clostridium novyi Herpes Viruses
Clostridium septicum Herpes simplex
Clostridium histolyticum
Varicella (Chicken pox)
Clostridium tertium Herpes Zoster (Shingles)
Clostridium. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzyl ecgonine, their derivatives and metabolites; ergot alkaloids, which include the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines; catecholamines, which includes ephedrine, L-dopa, **epinephrine**; narceine; papaverine; and metabolites of the above.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, **lidocaine**, procainamide, acetylprocainamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, chloramphenicol, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Polynucleotide--a compound or **composition** which is a polymeric nucleotide having in the natural state about 50 to 500,000 or more nucleotides and having in. . .

SUMM Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

SUMM . . . both compounds to associate with the same particle. This

possibly can be further reduced by utilizing particles of only one **composition** that are associated with either the photosensitizer or chemiluminescent compound or by using two types of particles that differ in **composition** so as to favor association of the photosensitizer with one type of particle and association of the chemiluminescent compound with. . .

SUMM . . . photosensitizer can be bound to the particle by attachment to a long hydrocarbon chain that is compatible with the particle **composition**. Frequently, at least one, and preferably two, hydrocarbon chains are employed having 8 to 20 or more carbon atoms.

SUMM . . . 150 nm latex beads stained with the photosensitizer tetraphenyl porphyrin, and coated with antibodies to HBsAg. After incubation of the **mixture** for one hour, the suspension is irradiated with 550 nm light. Following termination of the irradiation, the emitted light intensity. . .

SUMM . . . combined in one or more containers depending on the cross-reactivity and stability of the reagents. The kit comprises (1) a **composition** comprising a PACC bound to an sbp member. The kit can also include one or more additional sbp member reagents. . .

DETD . . . added 0.64 g (0.0056 mols) diglycolic anhydride 1A1 and the reaction was left 5 hr at ambient temperature. The reaction **mixture** was concentrated and extracted with 50 mL water, 50 mL ethyl acetate. The organic phase was washed with 0.1N HCl. . .

DETD . . . mmols) of N-hydroxysuccinimide. After stirring for 16 hr., 400 mg (1.85 mmols) of mono t-Boc 1,6-diaminohexane was added, and the **mixture** was stirred for an additional 4 hours at ambient temperature. The resulting **mixture** was concentrated to a thick solution and dissolved in 1:9 methanol-ethylacetate (100 mL) and extracted with water (3.times.50 ml), 0.1N. . . with (1:1) methanol/dichloromethane, concentrated, and the residue was dissolved in the minimum of methanol and added dropwise into water. The **mixture** was then centrifuged and the solid dried in vacuo, yielding 83% of 1A4.

DETD . . . was added 21.2 mg (0.185 mmols) methyl isocyanatoacetate and reaction was then left 24 hours at ambient temperature. The reaction **mixture** was added dropwise into a 10 ml stirring ethylacetate solution. The precipitated product was centrifuged, then resuspended in a minimum. . .

DETD The reaction **mixture** was concentrated to dryness and the product isolated using two Whatman PLC.sub.18 F plates 1000.mu., 20.times.20 cm eluant same as. . .

DETD . . . N-hydroxy succinimide were combined with 5 ml anhydrous dimethyl formamide and stirred at ambient temperature for 16 hours. The reaction **mixture** was added dropwise to a stirring solution of 13.6 mg (0.17 mmols) 21-atom long chain amine of 5-carboxyfluorescein 1A6 in. . .

DETD Using biotin-LC.sub.7 -NHS from Pierce Chemical Co., Rockford, Ill., three different levels of biotinylations (Ab.sub.IF :biotin in reaction **mixture**=1:10, 1:50, or 1:200) were performed. The Ab.sub.IF was in 0.05M NaPi, 0.05M NaCl/pH=7.8 at [IgG]=2.5 mg/ml. To this solution DMSO. . .

DETD . . . mL glass vial and warmed to 100.degree. on a laboratory hot plate. Benzyl alcohol (1.6 mL) was added and the **mixture** stirred magnetically. Stock latex suspension (2 mL, 38 nm carboxylate modified latex containing 10% solids) was added and the **mixture** allowed to equilibrate for 3 to 4 minutes. The nC.sub.10 solution (0.4 mL) was added slowly in 100 mL aliquots. Heating at 100.degree. was

continued for 5 minutes; then the **mixture** was allowed to cool to room temperature. After cooling, the **mixture** was applied to a column of Sephadex G-25 (2.5.times.15 cm) equilibrated with 50% aqueous ethanol. The latex containing fractions were. . .

DETD . . . mL Erlenmeyer flask and warmed to 110.degree. on a laboratory hot plate. Benzyl alcohol (8 mL) was added and the **mixture** stirred magnetically. The nC.sub.10 solution (2 mL) was added followed immediately by stock latex suspension (10 mL, 175 nm carboxylate. . . minutes while stirring vigorously. The flask was then placed in a room temperature water bath to cool. After cooling, the **mixture** was diluted with an equal volume of ethanol and immediately centrifuged at 15,000 rpm (Sorval, SA 600 rotor) for two. . .

DETD . . . 125 mL Erlenmeyer flask and warmed to 100.degree. on a laboratory hot plate. Benzonitrile (9 mL) was added and the **mixture** stirred magnetically. The BA-C.sub.18 solution (1 mL) was added followed immediately by stock latex suspension (10 mL, 175 nm latex. . . minutes while stirring vigorously. The flask was then placed in a room temperature water bath to cool. After cooling, the **mixture** was diluted with an equal volume of 50% aqueous ethanol and immediately centrifuged at 15,000 rpm (Sorval, SA 600 rotor). . .

DETD . . . and a small aliquot used for the reaction) together and incubating for three hours at 4.degree. C. In the reaction **mixture**, the molar ratio of the reactants was antibody:Biotin-LC.sub.7 -NHS=1:25. The uncoupled biotin was removed by Sephadex.RTM. G-25 column. The final. . .

DETD . . . of 100 mg/mL 6-carboxyfluorescein and 30.6 mg/mL of NHS in DMF,

0.4 mL of 275 mg/mL DCC was added. The **mixture** was stirred overnight at room temperature in the dark. The formed dicyclohexylurea was removed by filtration. The formation of F-NHS. . .

DETD . . . incubation at room temperature overnight with stirring in the dark. The molar ratio of F-NHS:LC.sub.9 was 1:40. Then, the reaction **mixture** was diluted 1/20 with 0.5M NaPi/pH 5.0, the pH of the **mixture** was adjusted to 5.0 by addition of phosphoric acid (1.0M) and the whole **mixture** was loaded onto a (2.5.times.10 cm) of BioRex-70.RTM. column, equilibrated in 0.5M NaPi/pH=5.0. After loading, the column was washed with. . .

DETD The following day, the reaction **mixture** was diluted with water and extracted from the reaction solution with methylene chloride. The methylene chloride extracts were dried over. . .

DETD The liposomes were prepared by methanol dilution method. Typically a **mixture** of lipids: Cholesterol (2.0 mg), DPPC (Avanti Polar Lipids, Alabaster, Ala.) (23.8), DPPG (Avanti Polar Lipids, Alabaster, Ala.) (6.5 mg),. . . liposomes were slowly added into stirred succinylated avidin-SH (prepared as described below) solution in buffer-B. After flushing with argon this **mixture** was mixed gently (no stirring bar) overnight at 4.degree. C. The excess maleimide groups were blocked with 2 mM mercaptosuccinic. . . acid to a final 5

mM concentration to block the excess thiol groups (30 min at 4.degree. C.). The reaction **mixture** was then concentrated to 2.5-3 ml by means of a Centriprep-30.RTM. device and the uncoupled avidin molecules were removed by. . .

DETD . . . less than 1% of the reaction volume), and the solution was incubated for 2 hours. The pH of the reaction **mixture** w-as kept at 7.4 by addition of 0.5M Na.sub.2 HPO.sub.4. The protected thiol groups (thioester) were liberated with hydroxylamine (0.1M,. . .

DETD . . . a stirred protein solution (15m of 0.02M Borax, 0.08M NaCl, 2 mg/ml 3G1 IgG (AbF), 8 mg/ml BSA/pH 8.9). The **mixture** was gently shaken (no stirring) overnight at 4.degree. C. The remaining

reactive groups on the beads, if any, were blocked. . .

DETD . . . of 0.005M NaPi/pH 5.8 and transferred into a stirred avidin solution (15 ml of 0.025M Borax, 1.33 mg/ml avidin/pH.sub.9.1). The **mixture** then was mixed gently at 4.degree. C. overnight. The avidin on the beads was succinylated by adding 20 ul of. . . at 4.degree. C. for 1 hour. The beads were blocked with 7 mg/ml BSA (the final concentration in the reaction **mixture**) for 60 min. at 4.degree. C. Finally the beads were washed three times with 0.05M NaPi, 0.15M NaCl/pH.sub.7.6 by centrifugation. . .

DETD . . . ml). N-hydroxysuccinimide (3.22 g, 28 mmole) was added as a solid to the DMF solution and allowed to dissolve. The **mixture** was then cooled in an ice bath. Dicyclohexyl carbodiimide (5.8 g, 28 mmole) was dissolved in dry DMF (10 ml) and added all at once to the cold DMF solution. The **mixture** was stirred at ice bath temperature for 30 min. and then allowed to come to room temperature. The course of. . .

DETD 4,9-Dioxa-1,12-dodecane diamine (25.5 g, 125 mmole) was diluted with dry DMF (10 ml). The fluorescein NHS ester reaction **mixture** was cooled in ice under an argon atmosphere and the diamine solution added dropwise over a period of 5 minutes.. . . The course of the reaction was followed by tlc using the above system. When the reaction was judged complete, the **mixture** was diluted with water (100 ml) and cooled in ice to precipitate dicyclohexylurea which was removed by filtration.

DETD . . . top of a silica gel column (2.5.times.25 cm) equilibrated with dichloromethane. The column was eluted with the above tlc solvent **mixture**. Fractions containing product were pooled and solvent removed on the rotovap. The residue was taken up in ethanol and filtered.. . .

DETD . . . (5.times.10.sup.12 beads/ml) and 100 .mu.L of biotin-LC.sub.21-F (varying amounts) in 0.05 NaPi, 0.15M NaCl, 4 mg/ml BSA/pH 7.6. This **mixture** was incubated at room temperature for 1.5 hours with shaking in the dark. Finally, each tube was illuminated with halogen.

.

.

DETD . . . buffer (0.05M NaPi, 0.15M NaCl, 4 mg/ml BSA/pH 7.6) and 50 .mu.l Ab.sub.1 (.alpha.HCG)-OD/BA-C.sub.18 reagent containing 5.times.10.sup.8 oil droplets. This **mixture** was incubated for one hour at room temperature in the dark. Then, 50 .mu.l of 2 .mu.g/ml Strepavidin-T680 in assay. . .

CLM What is claimed is:

72. A **composition** comprising a photochemically activated chemiluminescent compound (PACC) associated with a member of a specific binding pair.

73. The **composition** of claim 72 wherein said PACC contains an olefin group.

74. The **composition** of claim 72 wherein said PACC contains an olefin group and one or more electron donating substitutents in conjugation with. . .

75. The **composition** of claim 72 wherein said PACC is selected from the group consisting of 9-alkyline-N-alkyl acridans, enolethers, enamines, and 9-alkylidene xanthenes.

. . .

76. The **composition** of claim 72 wherein said sbp member is selected from the group consisting of receptors, ligands, and

polynucleotides.

77. A kit comprising in packaged combination: (1) a **composition** comprising a photochemically activatable chemiluminescent compound (PACC), having bound thereto a specific binding pair (sbp) member, and (2) a photosensitizer which is not in said **composition**.

L14 ANSWER 16 OF 45 USPATFULL

ACCESSION NUMBER:	94:5790 USPATFULL
TITLE:	Method of separation employing magnetic particles and second medium
INVENTOR(S):	Vorpahl, John, Livermore, CA, United States
PATENT ASSIGNEE(S):	Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5279936		19940118	
APPLICATION INFO.:	US 1989-455550		19891222	(7)

DISCLAIMER DATE:	20070619
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Nucker, Christine M.
ASSISTANT EXAMINER:	Preston, D. R.
LEGAL REPRESENTATIVE:	Leitereg, Theodore J., Bosse, Mark L.
NUMBER OF CLAIMS:	80
EXEMPLARY CLAIM:	1
LINE COUNT:	1535

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods are disclosed for separating a component of interest from a **mixture** containing the component of interest and other components. The method comprises contacting a first liquid medium containing the component of. . .

SUMM . . . in which the material to be separated is intrinsically magnetic. On the other hand, one or more components of a **mixture** can be rendered magnetic by the attachment of a magnetically responsive entity. In biochemical separations, materials of interest are generally.

. .

SUMM . . . bearing poly-ADP-ribose synthetase on their surface from unbound polynucleosomes, by causing specific antibodies to the synthetase to bind, combining the **mixture** with gold-labeled protein A and separating by sucrose gradient velocity sedimentation whereupon the gold bond polynucleosomes separated more rapidly. Courtoy,. . .

SUMM . . . Pat. No. 4,115,534. Functional magnetic particles formed by dissolving a mucopolysaccaride such as chitosan in acidified aqueous solution containing a **mixture** of ferrous chloride and ferric chloride is disclosed in U.S. Pat. No. 4,285,819. The microspheres may be employed to remove. . .

SUMM A diagnostic method employing a **mixture** of normally separable protein-coated particles is discussed in U.S. Pat. No. 4,115,535. Microspheres of acrolein homopolymers and copolymer with hydrophilic.

.

SUMM . . . method of the present invention is directed to the separation of a component of interest from other components in a **mixture** by causing the binding of the component of interest to magnetic

particles. Where the component of interest is present as. . .
interactions. A first liquid medium containing the component of interest
bound to magnetic particules and the other components of the **mixture** is contacted with, without mixing with, a second liquid medium that is of different density than and/or of different viscosity. . .

SUMM One embodiment of a method in accordance with the present invention is a
method for separating cells from a **mixture** containing the cells and other components. The method comprises layering a first liquid
medium containing the cells and other components. . .

DETD Component of interest (CI)--the compound or **composition** to be separated. The component of interest can be non-particulate or particulate. Non-particulate CI can be comprised of a member. . .

DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which include **cocaine** and benzoyl ecgonine, their derivatives and metabolites, ergot alkaloids, which include the diethylamide of lysergic
acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, and their metabolites.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . Spore-forming Bacilli
Phialophora jeanselmei
Bacillus anthracis Microsporum gypseum
Bacillus subtilis Trichophyton mentagrophytes
Bacillus megaterium
Keratinomyces ajelloi
Bacillus cereus Microsporum canis
Anaerobic Spore-forming Bacilli
Trichophyton rubrum
Clostridium **botulinum**
Microsporum adouini
Clostridium tetani Viruses
Clostridium perfringens
Adenoviruses
Clostridium novyi Herpes Viruses
Clostridium septicum
Herpes simplex
Clostridium histolyticum
Varicella (Chicken pox)
Clostridium tertium
Herpes Zoster (Shingles)
Clostridium. . .

DETD Receptor ("antiligand")--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, e.g., epitopic or determinant site. Illustrative receptors include. . .

DETD Polyionic reagent--a compound, **composition**, or material,

either inorganic or organic, naturally occurring or synthetic, having at least two of the same charge, either polyanionic. . .

DETD Releasing agent--a compound, **composition**, or material, either naturally occurring or synthetic, organic or inorganic, capable of reversing the non-specific binding between, i.e., dissociating, particulate. . .

DETD . . . to magnetic particles is involved, such binding will usually occur essentially instantaneously, and it is usually sufficient to allow the **mixture** to stand for 60 sec., frequently less than 15 sec.; preferably the magnetic field is applied immediately after contacting of. . .

DETD The invention further comprises a **composition** comprising (1) a first liquid medium containing magnetic particles to which are bound a component of interest (CI) and in. . . therewith (2) a second liquid medium having a different density and/or viscosity or immiscibility with the first liquid medium. The **composition** may further comprise a polyionic reagent of opposite charge to the magnetic particles. Alternatively, in the **composition** of the invention the magnetic particles can have a CI bound to an sbp member bound thereto.

CLM What is claimed is:

. . . method for separating a particulate biologic material (PBM), selected from the group consisting of microorganisms, cells, and organelles, from a **mixture** containing said PBM and other components, which method comprises: contacting a first liquid medium containing said PBM and said other. . .

19. A method for separating cells from a **mixture** containing said cells and other components, which method comprises: layering an aqueous medium containing said cells and said other components. . .

51. A **composition** comprising: (a) a first liquid medium containing magnetic particles wherein said magnetic particles are selected from the group consisting of. . .

52. The **composition** of claim 51 wherein said PBM is bound to said magnetic particles by means of charge-charge interactions.

53. The **composition** of claim 51 wherein said PBM is a cell or a microorganism.

. . . of microorganisms, cells, and organelles, wherein said assay comprises the step of separating said PBM from other components in a **mixture**, the improvement comprising: contacting a first liquid medium containing said PBM with a second liquid medium that is of different. . .

L14 ANSWER 17 OF 45 USPATFULL

ACCESSION NUMBER:	92:100755 USPATFULL
TITLE:	Method and apparatus for optically detecting presence of immunological components
INVENTOR(S):	Joseph, Jose P., Menlo Park, CA, United States Itoh, Kiminori, Tokyo, Japan
PATENT ASSIGNEE(S):	Teknekron Sensor Development Corporation, Menlo Park, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5169599		19921208

APPLICATION INFO.: US 1990-576359 19900830 (7)
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Johnston, Jill A.
LEGAL REPRESENTATIVE: Limbach & Limbach
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 730
DETD Analyte is used throughout this specification to refer to the compound or **composition** to be detected and measured, which is a mip and may be a ligand, which is mono- or polyepitopic, that. . .
DETD Receptor (antiligand)--any macromolecular compound or **composition** capable of recognizing (having an enhanced binding affinity to) a particular spatial or determinant site. Illustrative receptors include naturally occurring. . .
DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
DETD . . . group
Hemophilus influenzae,
H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Antinomyces naeslundii
Nocardia asteroides

Nocardia. . .
DETD . . . pollutants, and the like. Included are the alkaloids: morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .
DETD . . . is aminoalkylbenzenes with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, and their metabolites.
DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol,griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.
CLM What is claimed is:
8. The apparatus of claim 5 wherein said stepped layer comprises a **mixture** of iron phosphate and aluminum phosphate.

L14 ANSWER 18 OF 45 USPATFULL
ACCESSION NUMBER: 88:62445 USPATFULL
TITLE: Fluorescent conjugates bound to a support
INVENTOR(S): Khanna, Pyare, Mountain View, CA, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4774191		19880927
APPLICATION INFO.:	US 1986-826177		19860205 (6)

RELATED APPLN. INFO.: Division of Ser. No. US 1984-664121, filed on 23 Oct 1984, now patented, Pat. No. US 4588697 which is a division of Ser. No. US 1982-399506, filed on 19 Jul 1982, now patented, Pat. No. US 4481136 which is a division of Ser. No. US 1979-73158, filed on 7 Sep 1979, now patented, Pat. No. US 4351760
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Warden, Robert J.
ASSISTANT EXAMINER: Benson, Robert
LEGAL REPRESENTATIVE: Leitereg, Theodore J., Barrett, Carole F.
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
LINE COUNT: 1246
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
SUMM . . . H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis

Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . resorcinol and carboxylic acid or anhydride are combined in the presence of a Lewis acid e.g. zinc chloride, and the **mixture** heated at an elevated temperature for a sufficient time to provide the desired product. The product may then be purified. . .

DETD . . . phthalic anhydride (20.0 g) was dissolved in 20% fuming sulphuric acid (25 ml) and powdered iodine (0.5 g) added. The **mixture** was heated to 90.degree.-100.degree. and chlorine gas bubbled through the solution continuously. After 24 hrs heating, 0.5 g

more of. . .

DETD . . . been added, the reaction was checked by TLC. [TLC was taken by the following procedure: A sample of the reaction **mixture** was acidified with 6M H.sub.2 SO.sub.4 ; the excess KMnO.sub.4 was reacted with a saturated solution of oxalic acid; the. . .

DETD . . . pH1. The excess KMnO.sub.4 was removed by reaction with solid oxalic acid. Sulfuric acid (6M) was added to keep the **mixture** at pH 1 during the oxalic acid addition. The solution was concentrated on a Rotovap, yielding a white slurry. Hydrochloric. . .

DETD . . . In a 250 ml R.B. flask was dissolved the trichlorotriacid (II, 10 g) in 30 ml acetic anhydrde and the **mixture** heated at 140.degree.-45.degree. under N.sub.2 for 45 min. After cooling, the acetic anhydride was removed on a Rotovap under high. . .

DETD . . . wide mouth tube and heated in a preheated oil bath at 185.degree.-90.degree.. Anhydrous ZnCl.sub.2 (1 g) was added to the **mixture** and the heating continueed for 1.5 hrs with occasional mixing with a spatula, a hard red mass being obtained. The. . .

DETD The dried yellow powder was stirred with 200 ml of ethyl acetate overnight, the **mixture** filtered and the solids washed with 15 ml ethyl acetate. The ethyl acetate filtrate was concentrated on a Rotovap at. . .

DETD The above yellow solid **mixture** (6.0 g) was dissolved in 150 ml of freshly distilled THF (distilled over CaH.sub.2) and 3.0 g DCC added.

The. . . concentrated to dryness on a Rotovap at ambient temperature.

To the solid was then added 200 ml n-hexane and the **mixture** stirred for 2 hrs to remove excess DCC. The yellow solid was filtered and washed with 50 ml n-hexane. The remaining solid is a **mixture** of unreacted VI and anhydride VII as shown by TLC (solvent system THF:CH.sub.2 Cl.sub.2 60:40). (VI-2,7-dimethyl-9-(2',4'-dicarboxy-3',5',6'-trichlorophenyl)-6-hydroxy-3H-xanthen-3-one; VII-2,7-dimethyl-9-(3',4'-dicarboxy anhydride-2',5',6'-trichlorophenyl)-6-hydroxy-3H-xanthen-3-one).

DETD . . . in Example I was dissolved in dry THF (300 ml) and combined with 8.5 g of 3-.beta.-cholestanyl glycinate and the **mixture** stirred overnight at room temperature. The solvent was then removed and the residual solid stirred with water (150 ml) for 2 hrs. The resulting **mixture** was acidified with dil HCl to pH1 and stirring continued for 1 hr more in the cold room. The resulting. . . with 100 ml of ice-cold water and dried in vacuo. Its TLC (THF:CH.sub.2 Cl.sub.2 1:1) indicated it to be a **mixture** of only two major compounds. The yellow solid was absorbed on silica gel (30 g) with THF and dried. The dry powder was poured over a dry column of silica gel (200 g) and eluted

with THF:CH.sub.2 Cl.sub.2 **mixture** (1:4) with the elution followed by TLC. The faster moving spot eluant was collected and the solvent removed to give. . .

DETD . . . 8.0 during addition of NHS ester by adding a trace of solid Na.sub.2 CO.sub.3.) After the addition is complete, the **mixture** is stirred for 1.5 hrs at room temperature and then 1 ml of 2N NH.sub.2 OH (adjusted to pH 8.1) added and the **mixture** stirred for 1 hr. more in the cold room. After centrifugation of the reaction **mixture**, the supernatant solution was purified through Sephadex G-25 column using 0.05M PO.sub.4.sup.3- buffer at pH 8.0. The faster moving conjugate. . .

DETD B. To a **mixture** of the above ester (70 mg) in dry DMF (1 ml) containing triethylamine (100 .mu.l) was added the NHS ester. . .

DETD A. In a reaction flask was combined 1.35 g 4-methylresorcinol, 1 g

trimellitic anhydride and 100 mg ZnCl.sub.2 and the **mixture** heated at 195.degree.-200.degree. for 15 min. The resulting solid was macerated with water and filtered. The precipitate was dissolved in. . .

DETD Into a reaction flask was introduced 1.1 g of 4-(2'-carboxyethyl)resorcinol, 0.45 g phthalic anhydride and 250 mg ZnCl.sub.2 and the **mixture** heated at 160.degree.-70.degree. for 0.5 hr. After treating with water and filtering, the solid was dissolved in 5% NaOH, the. . .

DETD . . . procedures, into a reaction flask was introduced 2.6 g 4-(3'-carboxypropyl)resorcinol, 1.95 g 3,5,6-trichloro-1,2,4-benzenetricarboxylic acid and 100 mg ZnCl.sub.2 and the **mixture** heated at 180.degree.-85.degree. for 40 min. The **mixture** was worked up as previously described and the product purified by preparative TLC using CHCl.sub.3 :MeOH HOAc::80:20:1.

CLM What is claimed is:

1. A **composition** of matter consisting of a conjugate bonded to a Support, and of the formula: ##STR9## wherein: n.sup.3 is 1 to. . .

2. A **composition** of matter according to claim 1, wherein support is a polysaccharide.

L14 ANSWER 19 OF 45 USPATFULL

ACCESSION NUMBER:	87:20611 USPATFULL
TITLE:	Fluorescent protein binding assays with unsymmetrical fluorescein derivatives
INVENTOR(S):	Khanna, Pyare, San Jose, CA, United States Colvin, Warren, Redwood City, CA, United States
PATENT ASSIGNEE(S):	Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4652531		19870324
APPLICATION INFO.:	US 1984-587085		19840307 (6)
RELATED APPLN. INFO.:	Division of Ser. No. US 1981-340031, filed on 3 Mar 1981, now patented, Pat. No. US 4439356		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Marantz, Sidney		
LEGAL REPRESENTATIVE:	Rowland, Bertram I., Leitereg, Theodore J., Barrett, Carole F.		
NUMBER OF CLAIMS:	4		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1088		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . group

Hemophilus influenzae,
H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis

Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . resorcinol and carboxylic acid or anhydride are combined in the presence of a Lewis acid e.g. zinc chloride, and the **mixture** heated at an elevated temperature for a sufficient time to provide the desired product. The product may then be purified. . .

DETD A **mixture** of 2,4-dihydroxy-3,5-dichloro-2'-carboxy benzophenone (160 mg, 0.05 mmole) and 2-chloro-4-methoxyresorcinol (87 mg, 0.05 mmole) was heated in an open test tube. . .

DETD A **mixture** of the m- or p-carboxy substituted fluorescein (8 g) was added slowly to a hot (170.degree. conc. sodium hydroxide solution. . .

DETD . . . acid by heating at 180.degree. for 1 hr.) was added 14 g aluminum chloride and 3.4 g 4-chlororesorcinol and the **mixture** heated at 90.degree. for 6 hrs. After quenching with ice and 1N HCl, the black solution was extracted three times. . . purified by column chromatography on 200 g silica gel (Merck 60) and eluted with acetic acid:acetone:benzene (2:32:66), thereby isolating a **mixture** of isomers R.sub.f 0.4. The solid material was stirred with 1N HCl overnight, filtered and dried to give 2 g. . .

DETD . . . was filtered and cooled to ice-bath temperature (4.degree.). To this was added the ester solution prepared above and the reaction **mixture** stirred in the cold room overnight. After removing the solvents in vacuo, the residue was stirred in hexane, filtered and. . .

DETD A **mixture** of 15 mg of a product of Example XIII, 6 mg of N,N'-dicycloheyl carbodiimide and 3 mg of N-hydroxy succinimide. . .

L14 ANSWER 20 OF 45 USPATFULL

ACCESSION NUMBER: 87:18722 USPATFULL

TITLE: Energy absorbing particle quenching in light emitting competitive protein binding assays

INVENTOR(S): Liu, Yen-Ping, Santa Clara, CA, United States
Ullman, Edwin F., Atherton, CA, United States
Becker, Martin J., Palo Alto, CA, United States

PATENT ASSIGNEE(S): Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4650770		19870317
APPLICATION INFO.:	US 1983-559555		19831207 (6)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1981-258176, filed on 27 Apr 1981, now abandoned

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Kepplinger, Esther M.

ASSISTANT EXAMINER: Jay, Jeremy

LEGAL REPRESENTATIVE: Leitereg, Theodore J., Rowland, Bertram I.

NUMBER OF CLAIMS: 14

EXEMPLARY CLAIM: 1

LINE COUNT: 1292

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . nature of the assay can be affected. Where the analyte cannot be obtained in pure form, labeling of an impure **mixture** of the analyte can result in a substantial amount of background signal. For the most part, other than monoclonal antibodies, antiserum is a complex **mixture** of antibodies. Again, labeling of a heterogeneous antiserum can also result in a large background signal. Other considerations involve interference. . .

SUMM . . . analyte of interest and/or its specific binding partner or receptor may be present in less than about 50% of the **mixture**. Frequently, purification is difficult and sometimes impossible, so that one must deal with the impure **mixture**. In many assays, it is necessary to label either the analyte or the receptor, with the result

that much of. . .

SUMM . . . of the specific binding pair is bound, either covalently or non-covalently. By binding a plurality of molecules from an impure **mixture** of the specific binding member, there is a substantially high probability that at least one specific binding pair member will.

.

.

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor (anti-ligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule, i.e., determinant or epitopic site. Illustrative of receptors. . .

SUMM . . . relative to the analyte. Where one reagent is first combined with the sample suspected of containing the analyte and the **mixture** allowed to go substantially to equilibrium, usually there will be a relatively small excess of the analyte, while an excess.

. .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3

carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM The particles may be homogeneous or non-homogeneous, isotropic or anisotropic, in that the particle **composition** or quenching functionalities may be uniformly or non-uniformly dispersed, usually uniformly dispersed. The particles should provide sufficient quenching, so that. . .

SUMM . . . be adsorptive or non-adsorptive to proteins; the particles may be naturally occurring, synthetic or combinations thereof, a single material or **mixture** of materials and are normally chemically inert. The opaque particles absorb light in the wavelength of interest and are frequently. . .

DETD . . . R, V-5373, 1 mg of rabbit anti-human IgG in 1 ml PBS/NaN.sub.3 buffer, pH 7.4 is added. After sonicating the **mixture** for 1-2 min, the **mixture** is stirred overnight in the cold. The carbon particles are spun-down and the amount of protein in the supernatant checked. . .

DETD . . . series of tubes were prepared by adding in each tube 50 .mu.l

of a 1/8th dilution of a carbon particle **composition** to 1 ml of 0.1% ovalbumin/PBS/NaN.sub.3 buffer. A series of solutions of different concentrations of human IgG were prepared which. . . min, 250 .mu.l of the fluorescent beads conjugated to human IgG were added in the above buffer and the assay **mixture** incubated for an additional 90 min. The fluorescence of the assay **mixture** was then determined.

L14 ANSWER 21 OF 45 USPATFULL

ACCESSION NUMBER:	86:28171 USPATFULL
TITLE:	Method for performing fluorescent protein binding assay employing novel alkyl substituted fluorescent compounds and conjugates
INVENTOR(S):	Khanna, Pyare, Mountain View, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4588697		19860513
APPLICATION INFO.:	US 1984-664121		19841023 (6)

RELATED APPLN. INFO.:	Division of Ser. No. US 1982-399506, filed on 19 Jul 1982, now patented, Pat. No. US 4481136 which is a division of Ser. No. US 1979-73158, filed on 7 Sep 1979, now patented, Pat. No. US 4351760
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Nucker, Christine M.
LEGAL REPRESENTATIVE:	Barrett, Carole F., Leitereg, Theodore J., Rowland, Bertram I.
NUMBER OF CLAIMS:	5
EXEMPLARY CLAIM:	1
LINE COUNT:	1437

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide,

propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . resorcinol and carboxylic acid or anhydride are combined in the presence of a Lewis acid e.g. zinc chloride, and the **mixture** heated at an elevated temperature for a sufficient time to provide the desired product. The product may then be purified. . .

DETD . . . phthalic anhydride (20.0 g) was dissolved in 20% fuming sulphuric acid (25 ml) and powdered iodine (0.5 g) added. The **mixture** was heated to 90.degree.-100.degree. and chlorine gas bubbled through the solution continuously. After 24 hrs heating, 0.5 g more of. . .

DETD . . . been added, the reaction was checked by TLC. [TLC was taken by the following procedure: A sample of the reaction **mixture** was acidified with 6M H.sub.2 SO.sub.4 ; the excess KMnO.sub.4 was reacted with a saturated solution of oxalic acid; the. . .

DETD . . . pH1. The excess KMnO.sub.4 was removed by reaction with solid oxalic acid. Sulfuric acid (6M) was added to keep the **mixture** at pH 1 during the oxalic acid addition. The solution was concentrated on a Rotovap, yielding a white slurry. Hydrochloric. . .

DETD . . . In a 250 ml R.B. flask was dissolved the trichlorotriacid (II, 10 g) in 30 ml acetic anhydride and the **mixture** heated at 140.degree.-45.degree. under N.sub.2 for 45 min. After cooling, the acetic anhydride was removed on a Rotovap under high. . .

DETD . . . wide mouth tube and heated in a preheated oil bath at 185.degree.-90.degree.. Anhydrous ZnCl.sub.2 (1 g) was added to the **mixture** and the heating continued for 1.5 hrs with occasional mixing with a spatula, a hard red mass being obtained. The. . .

DETD The dried yellow powder was stirred with 200 ml of ethyl acetate overnight, the **mixture** filtered and the solids washed with 15 ml ethyl acetate. The ethyl acetate filtrate was concentrated on a Rotovap at. . .

DETD The above yellow solid **mixture** (6.0 g) was dissolved in 150 ml of freshly distilled THF (distilled over CaH.sub.2) and 3.0 g DCC added.

The. . . concentrated to dryness on a Rotovap at ambient temperature.

To the solid was then added 200 ml n-hexane and the **mixture** stirred for 2 hrs to remove excess DCC. The yellow solid was filtered and washed with 50 ml n-hexane. The remaining solid is a **mixture** of unreacted VI and anhydride VII as shown by TLC (solvent system THF:CH.sub.2 Cl.sub.2 60:40). (VI-2,7-dimethyl-9-(2',4'-dicarboxy-3',5',6'-trichlorophenyl)-6-hydroxy-3H-xanthen-3-one; VII-2,7-dimethyl-9-(3',4'-dicarboxy anhydride-2',5',6'-trichlorophenyl)-6-hydroxy-3H-xanthen-3-one).

DETD . . . in Example I was dissolved in dry THF (300 ml) and combined with 8.5 g of 3-.beta.-cholestanyl glycinate and the **mixture** stirred overnight at room temperature. The solvent was then removed and the residual solid stirred with water (150 ml) for 2 hrs. The resulting **mixture** was acidified with dil HCl to pH1 and stirring continued for 1 hr more in the cold room. The resulting. . . with 100 ml of ice-cold water and dried in vacuo. Its TLC (THF:CH.sub.2 Cl.sub.2 1:1) indicated it to be a **mixture** of only two major compounds. The yellow solid was absorbed on silica gel (30 g) with THF and dried. The dry powder was poured over a dry column of silica gel (200 g) and eluted with THF:CH.sub.2 Cl.sub.2 **mixture** (1:4) with the elution followed by TLC. The faster moving spot eluant was collected and the

solvent removed to give. . .

DETD . . . 8.0 during addition of NHS ester by adding a trace of solid Na.sub.2 CO.sub.3.) After the addition is complete, the **mixture** is stirred for 1.5 hrs at room temperature and then 1 ml of 2N NH.sub.2 OH (adjusted to pH 8.1) added and the **mixture** stirred for 1 hr. more in the cold room. After centrifugation of the reaction **mixture**, the supernatant solution was purified through Sephadex G-25 column using 0.05M PO.sub.4.sup.3- buffer at pH 8.0. The faster moving conjugate. . .

DETD B. To a **mixture** of the above ester (70 mg) in dry DMF (1 ml) containing triethylamine (100 .mu.l) was added the NHS ester. . .

DETD . . . for 1.5 hrs. To this solution was then added 0.3 ml of 3N NH.sub.2 OH solution (pH 8.0) and the **mixture** stirred for 45 min at room temperature. After centrifugation for 2 min, the supernatant was purified over G-25 Sephadex column. . .

DETD A. In a reaction flask was combined 1.35 g 4-methylresorcinol, 1 g trimellitic anhydride and 100 mg ZnCl.sub.2 and the **mixture** heated at 195.degree.-200.degree. for 15 min. The resulting solid was macerated with water and filtered. The precipitate was dissolved in. . .

DETD Into a reaction flask was introduced 1.1 g of 4-(2'-carboxyethyl)resorcinol, 0.45 g phthalic anhydride and 250 mg ZnCl.sub.2 and the **mixture** heated at 160.degree.-70.degree. for 0.5 hr. After treating with water, and filtering, the solid was dissolved in 5% NaOH, the. . .

DETD . . . procedures, into a reaction flask was introduced 2.6 g 4-(3'-carboxypropyl)resorcinol, 1.95 g 3,5,6-trichloro-1,2,4-benzenetricarboxylic acid and 100 mg ZnCl.sub.2 and the **mixture** heated at 180.degree.-85.degree. for 40 min. The **mixture** was worked up as previously described and the product purified by preparative TLC using CHCl.sub.3 :MeOH:HOAc::80:20:1.

L14 ANSWER 22 OF 45 USPATFULL

ACCESSION NUMBER:	85:11772 USPATFULL
TITLE:	Charge effects in enzyme immunoassays
INVENTOR(S):	Gibbons, Ian, Menlo Park, CA, United States Rowley, Gerald L., Cupertino, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4501692		19850226
APPLICATION INFO.:	US 1982-259629		19820501 (6)
RELATED APPLN. INFO.:	Division of Ser. No. US 1979-61099, filed on 26 Jul 1979, now patented, Pat. No. US 4287300		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Kight, John		
ASSISTANT EXAMINER:	Draper, Garnette D.		
LEGAL REPRESENTATIVE:	Rowland, Bertram I., Leitereg, Theodore J.		
NUMBER OF CLAIMS:	1		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1551		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . weight % of the total protein as the antibody of interest. When

preparing reagents which involve reactions with the antibody **composition**, the presence of the large amount of contaminant must be taken into account.

SUMM . . . system label will frequently be added prior to the charged member. The two reagents may be provided as a single **composition** or as separate compositions, depending upon the nature of the protocol.

SUMM . . . member to the analyte and incubating for a sufficient time for the system to at least approach equilibrium. To the **mixture** may then be added the charged member and at the same time or immediately thereafter, any additional components of the. . .

SUMM Analyte-the compound or **composition** to be measured, which may be a ligand, a single or plurality of compounds which share at least one common. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. determinant or epitopic site. Illustrative receptors include. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides

Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . Where the signal label is a large molecule such as an enzyme, and one is dealing with a relatively impure **mixture** containing either the ligand or receptor, one will normally provide for a plurality of substituents on the signal label, to. . .

SUMM . . . of a member of the specific binding pair is to minimize background effects. That is, if one employed an impure **mixture** of receptor, for example, and conjugated it to enzyme, if there was a one to one mole ratio of molecules in the impure **mixture** to molecules of enzyme, a substantial proportion of the enzyme would only be bound to impurities and if active would. . .

DETD . . . 150797, 8.5 mg/ml) was centrifuged for 10 min and the precipitate dissolved in 3 ml PBS, N.sub.3, Mg. To the **mixture** was then added 0.3 ml 100 mM dithioerythritol and the **mixture** incubated for 1 hr at room temperature, followed by chromatographing on a 2.6.times.75 cm Biogel A5M (200-400 mesh) column equilibrated. . .

DETD . . . 35.3 mg/ml solution of the antiHIgG was added 60 .mu.l (10 mg/ml DMF) of m-maleimidobenzoic acid NHS ester and the **mixture** allowed to stand at room temperature for 30 min, followed by the addition of 0.18 ml of 1M sodium acetate, pH5. The reaction **mixture** was then dialyzed 2.times.500 ml (degassed) 20 mM sodium acetate, pH5, 0.15M NaCl for 1 hr at room temperature. To. . . 0.5M phosphate, pH7, followed by 2 ml of the above reaction product at a concentration of 31.1 mg/ml and the **mixture** incubated at room temperature for 4 hrs. The reaction was terminated by the addition of 0.2 ml of 10 mM. . .

DETD . . . HIgG (35.3 mg protein/ml) was added 60 .mu.l of a 32 mM solution of m-maleimidobenzoic acid NHS ester and the **mixture** stirred at RT for 30 min. After adding 0.18 ml 1.0M NaOAc, pH5.0, the solution was dialyzed against 2.times.500 .mu.l. . . was added 0.2 ml of 0.5M PO.sub.4, pH7.0, followed by 2 ml of the above solution (31.1 .mu.g/ml) and the **mixture** incubated at RT for 4 hrs. The reaction was terminated by the addition of 0.2 ml 10 mM cysteine HCl. .

DETD . . . .mu.l. After 0.5 hr, 1 ml of a 1M hydroxylamine-HCl adjusted to

pH8 with sodium hydroxide was added and the **mixture** incubated at room temperature for 30 min before dialyzing 5.times.0.5 l. PBS, N.sub.3, Mg at room temperature overnight. The final. . .

DETD . . . 0.33 .mu.mole) was added 25 .mu.l of a 50 mg/ml fluorescein isothiocyanate DMF solution (9.2 fluorescein/protein mole ratio) and the **mixture** stirred at RT in the dark. The product was gel filtered on Sephadex G25M with PBS pH6.8 N.sub.3, Mg, to. . .

DETD . . . portion of silver oxide (20 g, 0.17 equiv.) was added. Stirring was continued for an additional twenty minutes. The reaction **mixture** was filtered through a Celite pad to remove the silver salts. The filtrate was evaporated to give a crude brown. . .

DETD The tetracetate IV (119 g, 0.226 mole) was added to methanol (1000 ml). The **mixture** was heated at 60.degree. until the solid dissolved. Triethylamine (25 ml) was then added, and the solution was heated at. . .

DETD The reaction **mixture** was allowed to cool. Ethanol (1 l) was added slowly to the stirred reaction **mixture**. The dextran began to precipitate after 350 ml had been added. Additional ethanol (2 l) was added to ensure complete. . .

DETD . . . of buffer with 0.05 ml of the appropriate concentration of human IgG and 0.10 ml of buffer and incubating the **mixture** for 3 hrs at room temperature. To the **mixture** was then added 0.1 ml of the succinylated antibody and 0.25 ml of buffer followed immediately (15 secs) by the. . .

DETD . . . enzyme conjugate (Ex 1D) with 50 .mu.l of HIgG in 0.2 ml buffer (PBS, N.sub.3, Mg, RSA) and incubating the **mixture** for 1 hr at RT. To the **mixture** was then added 100 .mu.l of the fluorescein labeled anti(HIgG) and 0.25 .mu.l buffer, the **mixture** incubated for 15 sec at RT and 100 .mu.l of 4 mM ONPG conjugated dextran (40,000 mw) in PBS, N.sub.3. . .

DETD In the next two assays, antienzyme was used as an inhibitor of enzyme which remains unbound to antigen. A **mixture** was prepared of 1.5 ml of the enzyme-antibody conjugate described previously and 1.5 ml of the succinylated antibody diluted 1:16. To 0.05 ml of the appropriate human IgG solution was added 0.10 ml of the above **mixture** and either (1) 0.05 ml antienzyme added within a few minutes or (2) the **mixture** incubated followed by the addition of 0.05 ml of the antienzyme. In each case, the mixtures were then incubated for. . .

L14 ANSWER 23 OF 45 USPATFULL

ACCESSION NUMBER:	84:62202 USPATFULL
TITLE:	Alkyl substituted fluorescent compounds and conjugates
INVENTOR(S):	Khanna, Pyare, Mountain View, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4481136		19841106
APPLICATION INFO.:	US 1982-399506		19820719 (6)
RELATED APPLN. INFO.:	Division of Ser. No. US 1979-73158, filed on 7 Sep 1979, now patented, Pat. No. US 4351760		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		

PRIMARY EXAMINER: Kight, John
ASSISTANT EXAMINER: Nutter, Nathan M.
LEGAL REPRESENTATIVE: Rowland, Bertram I., Leitereg, Theodore J.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 1275
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. ducreyi
H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli -Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethrophan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3

carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . resorcinol and carboxylic acid or anhydride are combined in the presence of a Lewis acid e.g. zinc chloride, and the **mixture** heated at an elevated temperature for a sufficient time to provide the desired product. The product may then be purified. . .

DETD . . . phthalic anhydride (20.0 g) was dissolved in 20% fuming sulphuric acid (25 ml) and powdered iodine (0.5 g) added. The **mixture** was heated to 90.degree.-100.degree. and chlorine gas bubbled through the solution continuously. After 24 hrs heating, 0.5 g more of. . .

DETD . . . been added, the reaction was checked by TLC. (TLC was taken by the following procedure: A sample of the reacton **mixture** was acidified with 6M H.sub.2 SO.sub.4 ; the excess KMnO.sub.4 was reacted with a saturated solution of oxalic acid; the. . .

DETD . . . pH1. The excess KMnO.sub.4 was removed by reaction with solid oxalic acid. Sulfuric acid (6M) was added to keep the **mixture** at pH 1 during the oxalic acid addition. The solution was concentrated on a Rotovap, yielding a white slurry. Hydrochloric. . .

DETD . . . In a 250 ml R.B. flask was dissolved the trichlorotriacid (II, 10 g) in 30 ml acetic anhydride and the **mixture** heated at 140.degree.-45.degree. under N.sub.2 for 45 min. After cooling, the acetic anhydride was removed on a Rotovap under high. . .

DETD . . . wide mouth tube and heated in a preheated oil bath at 185.degree.-90.degree.. Anhydrous ZnCl.sub.2 (1 g) was added to the **mixture** and the heating continued for 1.5 hrs with occasional mixing with a spatula, a hard red mass being obtained. The. . .

DETD The dried yellow powder was stirred with 200 ml of ethyl acetate overnight, the **mixture** filtered and the solids washed with 15 ml ethyl acetate. The ethyl acetate filtrate was concentrated on a Rotovap at. . .

DETD The above yellow solid **mixture** (6.0 g) was dissolved in 150 ml of freshly distilled THF (distilled over CaH.sub.2) and 3.0 g DCC added.

The. . . concentrated to dryness on a Rotovap at ambient temperature.

To the solid was then added 200 ml n-hexane and the **mixture** stirred for 2 hrs to remove excess DCC. The yellow solid was filtered and washed with 50 ml n-hexane. The remaining solid is a **mixture** of unreacted VI and anhydride VII as shown by TLC (solvent system THF:CH.sub.2 Cl.sub.2 60:40). (VI-2,7-dimethyl-9-(2',4'-dicarboxy-3',5',6'-trichlorophenyl)-6-hydroxy-3H-xanthen-3-one; VII-2,7-dimethyl-9-(3',4'-dicarboxy anydride-2',5',6'-trichlorophenyl)-6-hydroxy-3H-xanthen-3-one).

DETD . . . in Example I was dissolved in dry THF (300 ml) and combined with 8.5 g of 3-.beta.-cholestanyl glycinate and the **mixture** stirred overnight at room temperature. The solvent was then removed and the residual solid stirred with water (150 ml) for 2 hrs. The resulting **mixture** was acidified with dil HCl to pH1 and stirring continued for 1 hr more in the cold room. The resulting. . . with 100 ml of ice-cold water and dried in vacuo. Its TLC (THF:CH.sub.2 Cl.sub.2 1:1) indicated it to be a **mixture** of only two major compounds. The

yellow solid was absorbed on silica gel (30 g) with THF and dried. The dry powder was poured over a dry column of silica gel (200 g) and eluted with THF:CH.sub.2 Cl.sub.2 **mixture** (1:4) with the elution followed by TLC. The faster moving spot eluant was collected and the solvent removed to give. . .

DETD . . . 8.0 during addition of NHS ester by adding a trace of solid Na.sub.2 CO.sub.3.) After the addition is complete, the **mixture** is stirred for 1.5 hrs at room temperature and then 1 ml of 2N NH.sub.2 OH (adjusted to pH 8.1) added and the **mixture** stirred for 1 hr. more in the cold room. After centrifugation of the reaction **mixture**, the supernatant solution was purified through Sephadex G-25 column using 0.05M PO.sub.4.sup.3- buffer at pH 8.0. The faster moving conjugate. . .

DETD B. To a **mixture** of the above ester (70 mg) in dry DMF (1 ml) containing triethylamine (100 .mu.l) was added the NHS ester. . .

DETD . . . for 1.5 hrs. To this solution was then added 0.3 ml of 3N NH.sub.2 OH solution (pH 8.0) and the **mixture** stirred for 45 min at room temperature. After centrifugation for 2 min, the supernatant was purified over G-25 Sephadex column. . .

DETD A. In a reaction flask was combined 1.35 g 4-methylresorcinol, 1 g trimellitic anhydride and 100 mg ZnCl.sub.2 and the **mixture** heated at 195.degree.-200.degree. for 15 min. The resulting solid was macerated with water and filtered. The precipitate was dissolved in. . .

DETD Into a reaction flask was introduced 1.1 g of 4-(2'-carboxyethyl)resorcinol, 0.45 g phthalic anhydride and 250 mg ZnCl.sub.2 and the **mixture** heated at 160.degree.-70.degree. for 0.5 hr. After treating with water and filtering, the solid was dissolved in 5% NaOH, the. . .

DETD . . . procedures, into a reaction flask was introduced 2.6 g 4-(3'-carboxypropyl)resorcinol, 1.95 g 3,5,6-trichloro-1,2,4-benzenetricarboxylic acid and 100 mg ZnCl.sub.2 and the **mixture** heated at 180.degree.-85.degree. for 40 min. The **mixture** was worked up as previously described and the product purified by preparative TLC using CHCl.sub.3 :MeOH:HOAc::80:20:1.

L14 ANSWER 24 OF 45 USPATFULL

ACCESSION NUMBER:	84:17157 USPATFULL		
TITLE:	Unsymmetrical fluorescein derivatives		
INVENTOR(S):	Khanna, Pyare, San Jose, CA, United States Colvin, Warren, Redwood City, CA, United States		
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4439356		19840327
APPLICATION INFO.:	US 1981-240031		19810303 (6)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Kight, III, John		
ASSISTANT EXAMINER:	Nutter, Nathan M.		
LEGAL REPRESENTATIVE:	Rowland, Bertram I.		
NUMBER OF CLAIMS:	22		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1231		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . resorcinol and carboxylic acid or anhydride are combined in the presence of a Lewis acid e.g. zinc chloride, and the **mixture** heated at an elevated temperature for a sufficient time to provide the desired product. The product may then be purified. . .

DETD A **mixture** of 2,4-dihydroxy-3,5-dichloro-2'-carboxy benzophenone (160 mg, 0.05 mmole) and 2-chloro-4-methoxyresorcinol (87 mg, 0.05 mmole) was heated in an open test tube. . .

DETD A **mixture** of the m- or p-carboxy substituted fluorescein (8 g) was added slowly to a hot (170.degree. conc. sodium hydroxide solution. . .

DETD . . . acid by heating at 180.degree. for 1 hr.) was added 14 g aluminum chloride and 3.4 g 4-chlororesorcinol and the **mixture** heated at 90.degree. for 6 hrs. After quenching with ice and 1 N HCl, the black solution was extracted three. . . purified by column chromatography on 200 g silica gel (Merck 60) and eluted with acetic acid:acetone:benzene (2:32:66), thereby isolating a **mixture** of isomers R.sub.f 0.4. The solid material was stirred with 1 N HCl overnight, filtered and dried to give 2. . .

DETD . . . was filtered and cooled to ice-bath temperature (4.degree.). To this was added the ester solution prepared above and the reaction **mixture** stirred in the cold room overnight. After removing the solvents in vacuo, the residue was stirred in hexane, filtered and. . .

DETD A **mixture** of 15 mg of a product of Example XIII, 6 mg of N,N'-dicycloheyl carbodiimide and 3 mg of N-hydroxy succinimide. . .

L14 ANSWER 25 OF 45 USPATFULL

ACCESSION NUMBER: 83:27797 USPATFULL

TITLE: Test strip kits in immunoassays and compositions therein

INVENTOR(S): Litman, David J., Cupertino, CA, United States
Ullman, Edwin F., Atherton, CA, United States

PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4391904		19830705
APPLICATION INFO.:	US 1981-255022		19810417 (6)

DISCLAIMER DATE: 19981110
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1979-106620, filed on 26 Dec 1979, now patented, Pat. No. US 4299916
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wiseman, Thomas G.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1,6
LINE COUNT: 2355
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic, usually antigenic or haptenic, a single or. . .

DETD Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic or determinant site. Illustrative receptors include. . .

DETD . . . employed to which is also bound receptor. The sample containing polyepitopic ligand analyte is combined with the antibody-bound-surface and the **mixture** incubated for a sufficient time, so that a detectable amount of analyte would have had an opportunity to bind. To the **mixture** is then added the enzyme-bound-antiligand and the **mixture** incubated again for a sufficient time for a detectable amount of the enzyme conjugate to bind to ligand bound to. . .

DETD . . . with enzyme-bound-receptor and the hapten-bound-surface to which is bonded a precursor to the signal generating compound and, as appropriate, the **mixture** incubated for a sufficient time for the hapten to bind to the receptor and the enzyme-bound-receptor to the surface. The. . .

DETD . . . be bound to the surface (enzyme and antibody-bound-surface). The surface would be combined with a polyepitopic antigen analyte and the **mixture** incubated for a sufficient time for the antigen to bind to the receptor on the surface. Normally, the binding of the antigen will be performed in the undiluted sample. To the **mixture** may then be added as a single reagent the enzyme catalyst bound receptor, the solute, which is the substrate for. . .

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD . . . H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus

Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia. . .

DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, ctecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

DETD The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . will involve aralkylamine structures, which may or may not be a part of a heterocyclic structure, e.g. alkaloids, phenobarbitol, dilantin, **epinephrine**, L-dopa, etc. While there is some similarity in structure, the compounds vary widely as to activity.

DETD . . . have different physical characteristics, can be of different chemical compositions and may be of one or more compositions as a **mixture** of compositions or laminates or combinations thereof. The particular surface will interact with the signal generating compound by desolubilization of. . .

DETD . . . hydrophilic, i.e. polar or non-polar, preferably hydrophilic, may be coated with a thin mono- or polymolecular layer of a different

composition or uncoated, may be a single material or a plurality of materials, particularly as laminates or fibers, may be woven,. . .

DETD . . . and 12 .mu.moles of EDCI in a total volume of about 12.1 ml in DMF. After combining the reagents, the **mixture** was flushed with nitrogen and stirred overnight in a cold room. To 0.5 ml HRP (2 mg) in 50 mM. . . sodium carbonate (pH 9.5) was added 150 ml DMF, followed by 300 .mu.l of the above ester solution and the **mixture** allowed to stand overnight at 4.degree.. The reaction **mixture** was then applied to a 2.times.30 cm column of G50 Sephadex and eluted with 0.05 M tris, pH 7.6, 0.1. . .

DETD . . . in 0.2 M borate, pH 8.5, 0.5 M NaCl, 0.1 M NaBH.sub.3 CN was added to the disks and the **mixture** allowed to stand overnight at 4.degree.. To the **mixture** was then added 1.4 ml 50 mM Bicine buffer, pH 8.5, containing 2 mg NaBH.sub.4 and the **mixture** allowed to stand for 3 hrs. at room temperature, followed by termination by washing the disks in 1 M borate,. . .

DETD . . . 0.94 .mu.l of buffer, the buffer being 50 mM tris, pH 7.6, 100 mM KCl, and 0.1 mg/ml BSA. The **mixture** was incubated for 5 hrs followed by the addition of HRP-M or Rig-HRP in 1 ml of the appropriate reaction. . .

DETD . . . solution at varying concentrations. To the tube was then added a 6 mm disk of Ab.sub.M GO (2:1) and the **mixture** incubated at 3 hrs at room temperature.

DETD . . . phosphate, pH 6.0, 200 mM KCl, 0.1 mg/ml o-dianisidine) and 10 .mu.l 90 mM hydrogen peroxide were added and the **mixture** allowed to react for 5 mins, followed by washing; in the second method, the same procedure was employed, except that. . .

DETD To the paper was then added 2 ml 2 mg/ml NaBH.sub.4 in the same buffer and the **mixture** allowed to stand for 1 hr at RT. The paper was then washed with water and buffer, then immersed in. . .

DETD . . . 0.2 M NaCl and 0.1 mg/ml o-dianisidine. To the solution was then added 4 .mu.l HRP-M (20 .mu.g/ml) and the **mixture** followed to stand for 30 min at RT and the tests repeated with 15 .mu.l HRP-M and a reaction time. . .

DETD . . . with the other samples. Thus, the assay is able to detect minute amounts of morphine in the complex proteinaceous urine **mixture**.

DETD . . . 10 .mu.l of 3.9 mg/ml catalase and incubating for 60 min at RT with a developer solution of the following **composition**: 50 mM bicine, pH 8.0, 200 mM KCl, 2 mg/ml BSA, 50 mM .beta.-D-glucose and 0.1 mg/ml 4-Cl-1-naphthol. The difference. . .

DETD . . . disks washed, and 0.5 ml buffer added plus 50 .mu.l of a 13.8 .mu.g/ml solution of Ab.sub.HIg -HRP (DAKO). The **mixture** was then incubated for 3 hrs at room temperature followed by the addition of 1 ml of 100 mM phosphate,. . .

DETD . . . 0.28 ml HRP (1.5 mg), 0.1 ml 1 M Na.sub.2 CO.sub.3, pH 9.5, and 0.3 ml H.sub.2 O and the **mixture** stirred overnight. After centrifuging to remove insoluble material, the supernatant was dialyzed against 0.1 M NaHCO.sub.3, 0.5 M NaCl (4. . .

DETD . . . ml of a protein solution containing 3.83 A.sub.280 /cm glucose oxidase and 0.75 mg of antisera for tetrahydrocannabinol and the **mixture** allowed to react for 1 hr at RT followed by the addition of 0.5 ml of a 4 mg/ml NaBH.sub.4 solution and the reaction **mixture** allowed to stand for 1.5 hr at RT, turning the disk every 20 min. The disk was then washed with. . .

L14 ANSWER 26 OF 45 USPATFULL

ACCESSION NUMBER: 83:9021 USPATFULL
TITLE: Macromolecular environment control in specific receptor assays
INVENTOR(S): Litman, David J., Palo Alto, CA, United States
Harel, Zvi, Stanford, CA, United States
Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4374925		19830222
APPLICATION INFO.:	US 1981-232777		19810209 (6)

DISCLAIMER DATE: 19980623
RELATED APPLN. INFO.: Division of Ser. No. US 1978-964099, filed on 24 Nov 1978, now patented, Pat. No. US 4275149, issued on 23 Jun 1981
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wiseman, Thomas G.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
LINE COUNT: 2405
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaoilds, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . and washed in 1 mM HCl, 200 ml) in 0.1 M sodium bicarbonate, pH

8.1, 0.5 M NaCl and the **mixture** stirred at 4.degree. for six hours, followed by stirring for two hours at room temperature. To the solution was then. . . added 0.25 ml of 1 M 2-aminopropanol, pH 8.0 and the reaction allowed to stir overnight at 4.degree.. The reaction **mixture** was then washed by centrifugation 3.times.2 ml 0.1 M borate, pH 8.5, 1 M NaCl, followed by 2.times.2 ml of. . .

DETD . . . and 50 .mu.l of a 10 mg/ml solution (added in 25 .mu.l aliquots) of meta-maleimidobenzoic acid NHS ester and the **mixture** stirred for 30 min at room temperature. The reaction **mixture** was then chromatographed on a 2.5.times.25 cm G50 column equilibrated with N.sub.2 purged 0.1 M phosphate, pH 6, 10 mM. . .

10 mM EDTA containing 13.5 mg HK, was added 50 .mu.l 2 M glucose and 0.4 ml DMF and the **mixture** stirred under nitrogen at room temperature. To the solution was added 100 .mu.l in four aliquots of a 20 mg/ml. . . for reaction to occur, 0.4 ml of 1 M hydroxylamine, pH 7.5, was added with stirring under nitrogen and the **mixture** stirred for 60 min at room temperature.

DETD The reaction **mixture** was then chromatographed on a 2.5.times.25 cm G50 column in 0.1 M phosphate, pH 6, 10 mM EDTA, nitrogen purged,. . . mg), the aqueous medium being 0.1 M phosphate, pH 6, 10 mM EDTA, 30 mM glucose, and nitrogen purged. The **mixture** was allowed to react at 4.degree. for 48 hrs.

DETD The reaction **mixture** was then chromatographed on a BiogelA5M column in 0.1 M phosphate, pH 7, 10 mM EDTA, 2 mM .beta.-Me 0.02% azide, the column nitrogen purged, and the **mixture** applied to the column in 6 ml and eluted in 3.5 ml fractions. Fractions 45 to 68 were pooled and. . .

DETD . . . 155 .mu.l of 2 M hydroxylamine HCl pH 8.0 were added. After stirring for an additional 2 hrs, the reaction **mixture** was dialyzed at 4.degree. against 350 ml of 0.05 M sodium phosphate buffer pH 7.0 over 72 hrs with six. . .

DETD . . . 1.0 M hydroxylamine HCl pH 7.5 was added and the stirring was continued for an additional 10 min. The reaction **mixture** was chromatographed on 0.9.times.10.5 cm G-25 fine Sephadex column (degassed and saturated with argon) with 0.05 M sodium phosphate buffer,. . .

DETD . . . stirring, the reaction was terminated by addition of 0.4 ml of 1 M sodium acetate buffer pH 5.0. The reaction **mixture** was chromatographed on 0.9.times.2.5 cm G-25 fine Sephadex column with 0.02 M sodium acetate buffer, pH 5.0; fractions of 1.0. . .

DETD . . . under nitrogen and the RIgG-SH solution (Example 4) was added slowly. The pH was brought to 6.7 and the reaction **mixture** was stirred at r.t. for 3 hrs and overnight at 4.degree.. After addition of 0.2 ml 0.01 M mercaptoethanol solution and stirring at r.t. for 30 min, the reaction **mixture** was kept over 72 hrs. at 4.degree.. The solution was concentrated to 1 ml volume in Amicon through PM30 Diaflo.RTM.. . .

DETD . . . and 12 ml chlorotrimethylsilane were stirred in 80 ml dry pyridine overnight at r.t. under an argon atmosphere. The reaction **mixture** was evaporated to dryness under reduced pressure, ether was added and the white crystals were removed by filtration. The supernatant. . .

DETD . . . stirred at r.t. for 60 hrs. Water (26 ml) was added and the solution was stirred for 30 min. The **mixture** was evaporated to dryness, 750 ml of methanol, 130 ml of water and 5.3 ml of acetic acid were added and the **mixture** was stirred overnight. The precipitate was filtered and the methanol was evaporated under reduced

pressure to give 8 g of. . .

DETD A reaction **mixture** was prepared by combining 4 ml HIgG (8.34 mg/ml, 50 mM phosphate buffer, pH 7.0), 2.17 ml phosphate buffer, pH. .

. at room temperature to the reaction was added 1 ml 1 M NaOAc to adjust the pH to 5. The **mixture** was then chromatographed on Sephadex G25-F (2.4.times.20 cm), eluted with 20 mM NaOAc, pH 5.0, containing 0.15 M NaCl at. . .

DETD . . . anti(HIgG) in 0.1 M NaHCO.sub.3, pH 8.1, 0.5 M NaCl and 0.9 g CNBr activated Sepharose 4B heads and the **mixture** stirred at 4.degree. for 6 hrs, followed by stirring at R.T. for 2 hrs. To the **mixture** was then added 0.1 volume 1 M 2-aminopropanol, pH 8.0 and the **mixture** stirred overnight at 4.degree.. By employing radioactive Ranti(HIgG), it was found that 6.6 mg had coupled.

DETD . . . was added 2 g dextran T2000 (Pharmacia), followed by the addition of 10 ml 2.5 N aq. NaOH, and the **mixture** heated at 70.degree.-75.degree. for 1.5 hr and allowed to stand overnight. To the **mixture** was added 2 ml glac. HOAc and the **mixture** then dialyzed against 10 l 5% aq. HOAc (4.times.24 hr) and then against deionized H.sub.2 O, 10 l. (4.times.24 hrs).. . .

DETD . . . N,N'-bis-(3-aminopropyl)piperazine and 18 g (90 mmole) EDCI and

the solution allowed to stand at R.T. for 24 hrs. The reaction **mixture** was then dialyzed against 12 l. deionized water containing 150 g K.sub.2 HPO.sub.4 and 75 g KH.sub.2 PO.sub.4 (4.times.24 hrs). . .

DETD c. To 10 ml DMF was added 387 mg 2-nitro-5-carboxyphenyl-.beta.-galactoside, 249 mg EDCI and 151 mg N-hydroxy sucnimide and the **mixture** stirred at R.T. for 1 hr. To 10 ml of aqueous solution containing the aminosubstituted dextran prepared above (9.2 mM in amino groups) was added 2.5 ml of the NHS ester prepared above and the reaction **mixture** stored at R.T. for 24 hrs. The reaction **mixture** was dialyzed against water (4.times.) and the product assayed for o-nitrophenyl-.beta.-galactoside groups (ONPG). The product was found to be 7.0. . .

DETD . . . .mu.l of beads is added to 50 .mu.l of incubation buffer containing varying amounts of human IgG. To the incubation **mixture** is added 8 .mu.l of the rabbit anti(HIgG)-HK conjugate and the samples incubated for 30 min at 37.degree.. To the **mixture** is then added 1 ml of assay buffer, the sample vortexed for approximately 3 sec and immediately aspirated into a. . .

DETD . . . Mg is added to a final volume of 1.05 ml which is promptly aspirated into a spectrophotometer cell. The reaction **mixture** is then read at 37.degree. at 420 nm by taking readings at 10 and 40 sec

after addition of the. . .

DETD . . . in that order. Incubate at R.T. for 3 hrs. Add 0.1 ml substrate

and 0.4 ml buffer and aspirate the **mixture** into a spectrophotometer cell and read at 37.degree. at 10 and 40 sec after adding the substrate. The following table. . .

L14 ANSWER 27 OF 45 USPATFULL

ACCESSION NUMBER: 82:62955 USPATFULL

TITLE: Concentrating zone method in heterogeneous immunoassays

INVENTOR(S): Tom, Henry K., La Honda, CA, United States
Rowley, Gerald L., Cupertino, CA, United States

PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4366241		19821228	
APPLICATION INFO.:	US 1980-176177		19800807	(6)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Wiseman, Thomas G.			
LEGAL REPRESENTATIVE:	Rowland, Bertram I.			
NUMBER OF CLAIMS:	34			
EXEMPLARY CLAIM:	1,15,22			
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 1 Drawing Page(s)			
LINE COUNT:	2456			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Analyte--the compound or **composition** to be measured, which is a mip and may be a ligand, which is mono- or polyepitopic, that is, having. . .

DETD (b) Receptor (antiligand)--any macromolecular compound or **composition** capable of recognizing (having an enhanced binding affinity to) a particular spatial and polar organization of a molecule, i.e. epitopic. . .

DETD . . . solutes diffusing to and away from a layer immersed in a liquid. Thus the layer encounters a continuously changing solution **composition** as solute becomes bound to the layer or dissolves into the liquid. In the subject invention, the mip containing layer in contact with the solution continuously contacts substantially the same solution **composition** as the solution diffuses through the layer. Thus, the concentrations of solutes in the solution in the mip containing layer. . .

DETD . . . manner in which the time for diffusion of the solutions through the immunosorbing zone may be controlled will involve the **composition**, construction, size and shape of the immunosorbing and liquid absorbing zones, the temperature, the solvent, and the like. In view. . .

DETD . . . the substrate solution could be combined with the sample and enzyme-antigen solution followed by immersing the assay device in the **mixture**.

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD Clostridium **botulinum**

DETD . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

DETD . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

DETD The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

DETD The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide,

propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . and 12.mu. moles of EDCI in a total volume of about 1.2 ml in DMF. After combining the reagents, the **mixture** was flushed with nitrogen and stirred overnight in a cold room. To 0.5 ml HRP (2 mg) in 50 mM. . . sodium carbonate (pH 9.5) was added 150 ml DMF, followed by 300 .mu.l of the above ester solution and the **mixture** allowed to stand overnight at 4.degree.. The reaction **mixture** was then applied to a 2.times.30 cm column of G50 Sephadex and eluted with 0.1 M phosphate, pH 7.6, 0.1. . .

DETD . . . the appropriate protein solution in 0.55 M borate, pH 8.5, 0.2 M NaCl, was added to the disks and the **mixture** allowed to stand for 2 hours at room temperature. To the **mixture** was then added 3.0 ml of a 1 mg/ml NaBH.sub.4 solution and the **mixture** allowed to stand for 3 hrs. at room temperature, followed by termination by extensively washing the disks in 0.055 M. . .

CLM What is claimed is:

. . . said assay device, wherein said immunosorbing zone is immersed in said sample solution; flowing said sample solution of substantially constant **composition** through said immunosorbing zone; whereby said solutions migrate through said immunosorbing zone into said liquid absorbing zone resulting in an. . .

. . . precursor, wherein said immunosorbing zone is substantially completely immersed in said sample solution; flowing said sample solution having substantially constant **composition** through said immunosorbing zone; whereby said solutions migrate through said immunosorbing zone into said liquid absorbing zone and said signal. . .

L14 ANSWER 28 OF 45 USPATFULL

ACCESSION NUMBER:	82:47270 USPATFULL
TITLE:	Novel alkyl substituted fluorescent compounds and polyamino acid conjugates
INVENTOR(S):	Khanna, Pyare, Mountain View, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4351760		19820928	
APPLICATION INFO.:	US 1979-73158		19790907	(6)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Schain, Howard E.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	7
EXEMPLARY CLAIM:	1
LINE COUNT:	1390

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan,

their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . resorcinol and carboxylic acid or anhydride are combined in the presence of a Lewis acid e.g. zinc chloride, and the **mixture** heated at an elevated temperature for a sufficient time to provide the desired product. The product may then be purified. . .

DETD . . . phthalic anhydride (20.0 g) was dissolved in 20% fuming sulphuric acid (25 ml) and powdered iodine (0.5 g) added. The **mixture** was heated to 90.degree.-100.degree. and chlorine gas bubbled through the solution continuously. After 24 hrs heating, 0.5 g more of. . .

DETD . . . been added, the reaction was checked by TLC. [TLC was taken by the following procedure: A sample of the reaction **mixture** was acidified with 6 M H.sub.2 SO.sub.4 ; the excess KMnO.sub.4 was reacted with a saturated solution of oxalic acid;. . .

DETD . . . The excess KMnO.sub.4 was removed by reaction with solid oxalic acid. Sulfuric acid (6 M) was added to keep the **mixture** at pH 1 during the oxalic acid addition. The solution was concentrated on a Rotovap, yielding a white slurry. Hydrochloric. . .

DETD . . . In a 250 ml R.B. flask was dissolved the trichlorotriacid (II, 10 g) in 30 ml acetic anhydride and the **mixture** heated at 140.degree.-45.degree. under N.sub.2 for 45 min. After cooling, the acetic anhydride was removed on a Rotovap under high. . .

DETD . . . wide mouth tube and heated in a preheated oil bath at 185.degree.-90.degree.. Anhydrous ZnCl.sub.2 (1 g) was added to the **mixture** and the heating continued for 1.5 hrs with occasional mixing with a spatula, a hard red mass being obtained. The. . .

DETD The dried yellow powder was stirred with 200 ml of ethyl acetate overnight, the **mixture** filtered and the solids washed with 15 ml ethyl acetate. The ethyl acetate filtrate was concentrated on a Rotovap at. . .

DETD The above yellow solid **mixture** (6.0 g) was dissolved in 150 ml of freshly distilled THF (distilled over CaH.sub.2) and 3.0 g DCC added.

The. . . concentrated to dryness on a Rotovap at ambient temperature.

To the solid was then added 200 ml n-hexane and the **mixture** stirred for 2 hrs to remove excess DCC. The yellow solid was filtered and washed with 50 ml n-hexane. The remaining solid is a **mixture** of unreacted VI and anhydride VII as shown by TLC (solvent system THF:CH.sub.2 Cl.sub.2 60:40). (VI-2,7-dimethyl-9-(2',4'-dicarboxy-3',5',6'-trichlorophenyl)-6-hydroxy-3H-xanthen-3-one;

VII-2,7-dimethyl-9-(3',4'-dicarboxy
anhydride-2',5',6'-trichlorophenyl)-
6-hydroxy-3H-xanthen-3-one).

DETD . . . in Example I was dissolved in dry THF (300 ml) and combined with 8.5 g of 3-.beta.-cholestanyl glycinate and the **mixture** stirred overnight at room temperature. The solvent was then removed and the residual solid stirred with water (150 ml) for 2 hrs. The resulting **mixture** was acidified with dil HCl to pH 1 and stirring continued for 1 hr more in the cold room. The. . . with 100 ml of ice-cold water and dried in vacuo. Its TLC (THF:CH.sub.2 Cl.sub.2 1:1) indicated it to be a **mixture** of only two major compounds. The yellow solid was absorbed on silica gel (30 g) with THF and dried. The dry powder was poured over a dry column of silica gel (200 g) and
eluted
with THF:CH.sub.2 Cl.sub.2 **mixture** (1:4) with the elution followed by TLC. The faster moving spot eluant was collected and the solvent removed to give. . .

DETD . . . 8.0 during addition of NHS ester by adding a trace of solid Na.sub.2 CO.sub.3.) After the addition is complete, the **mixture** is stirred for 1.5 hrs at room temperature and then 1 ml of 2 N
NH.sub.2
OH (adjusted to pH 8.1) added and the **mixture** stirred for 1 hr. more in the cold room. After centrifugation of the reaction **mixture**, the supernatant solution was purified through Sephadex G-25 column using 0.05 M PO.sub.4.sup.3- buffer at pH 8.0. The faster moving. . .

DETD B. To a **mixture** of the above ester (70 mg) in dry DMF (1 ml) containing triethylamine (100 .mu.l) was added the NHS ester. . .

DETD . . . 1.5 hrs. To this solution was then added 0.3 ml of 3 N
NH.sub.2
OH solution (pH 8.0) and the **mixture** stirred for 45 min at room temperature. After centrifugation for 2 min, the supernatant was purified over G-25 Sephadex column. . .

DETD A. In a reaction flask was combined 1.35 g 4-methylresorcinol, 1 g trimellitic anhydride and 100 mg ZnCl.sub.2 and the **mixture** heated at 195.degree.-200.degree. for 15 min. The resulting solid was macerated with water and filtered. The precipitate was dissolved in. .
.

DETD Into a reaction flask was introduced 1.1 g of 4-(2'-carboxyethyl)resorcinol, 0.45 g phthalic anhydride and 250 mg
ZnCl.sub.2
and the **mixture** heated at 160.degree.-70.degree. for 0.5 hr. After treating with water and filtering, the solid was dissolved in 5% NaOH, the. . .

DETD . . . procedures, into a reaction flask was introduced 2.6 g 4-(3'-carboxypropyl)resorcinol, 1.95 g 3,5,6-trichloro-1,2,4-benzenetricarboxylic acid and 100 mg ZnCl.sub.2 and the **mixture** heated at 180.degree.-85.degree. for 40 min. The **mixture** was worked up as previously described and the product purified by preparative TLC using CHCl.sub.3 :MeOH:HOAc::80:20:1.

CLM What is claimed is:

5. A **composition** of matter consisting of a conjugate bonded to a Support, and of the formula: ##STR10## wherein: n.sup.3 is 1 to. .
.

6. A **composition** of matter according to claim 5, wherein said support is a polysaccharide.

7. A **composition** of matter according to any of claims 5 and 6, wherein A.sup.2 is a poly(amino acid) of from about 2,000. . .

L14 ANSWER 29 OF 45 USPATFULL

ACCESSION NUMBER:	82:21571 USPATFULL
TITLE:	Enzyme-aminoglycoside conjugates
INVENTOR(S):	Rowley, Gerald L., San Jose, CA, United States Leung, Danton, Campbell, CA, United States Singh, Prithipal, Santa Clara, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4328311		19820504
APPLICATION INFO.:	US 1980-125713		19800228 (6)

RELATED APPLN. INFO.: Division of Ser. No. US 1978-876772, filed on 10 Feb 1978, now patented, Pat. No. US 4220722, issued on 2 Sep 1980

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Shapiro, Lionel M.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	17
EXEMPLARY CLAIM:	1
LINE COUNT:	1430

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of interest, but the analyte having the protective groups. This may result in substantially reducing the specificity of the antibody **composition** for the analyte of interest.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecogonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, methyldopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM . . . miscellaneous individual drugs which include methadone, phenoxybenzamine and related haloalkylamines, tolamol, sotalol, guanethide, meprobamate, serotonin, meperidine, chlorcyclazine, chlorpheniramine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, methotrexate, aminopterin, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Depending upon the particular compounds involved, other ancillary materials may also be included in the reaction **mixture**.

DETD . . . hydrochloride (ECDI) were added with stirring. After stirring for a short while the temperature was raised to 0.degree. and the **mixture** stirred for an additional 5 hrs., followed by storage at 4.degree. for about 30 hrs.

DETD The second fraction was evaporated to dryness to yield an oily solid weighing 57 mg. The product was a **mixture** of starting materials and product. Some removal of the bromoacetic acid was achieved

by dissolving the **mixture** in chloroform, extracting with 3-4 ml portions of water and then extracting the aqueous portions with 3-4 ml portions of. . .

DETD The entire product was dissolved in 200 .mu.l of anhydrous DMF and 150 .mu.l of anhydrous diglyme and the **mixture** stirred overnight under argon. To an aliquot of 89 .mu.l was added 50 .mu.l of anhydrous DMF containing 10 .mu.M. . .

DETD . . . phosphate followed by the further addition of 93 .mu.l of water to provide a total volume of 1.03 ml. The **mixture** was cooled to 0.degree. and the addition of the above NHS ester solution added slowly with vigorous stirring in aliquot. . .

DETD . . . aminoethanethiol (39 mg, 0.5 mmol) and triethylamine (210 ml, 1.5 mmol) in 1.0 ml of anhydrous dimethylformamide under nitrogen. The **mixture** was allowed to warm to room temperature over 11/2 hours, the solvent was removed in vacuo at 40.degree., and the. . . taken up in 3 ml of water and treated with 20 ml of 0.10 M sodium carbonate. Extraction of the **mixture** with ethyl acetate, washing with water, and evaporation in vacuo yielded a glass. To this glass were added under nitrogen,. . .

DETD . . . homogeneous enzyme immunoassay. By adding the antibody to a sample containing morphine or a morphine derivative i.e. codeine, when the **mixture** is added to the enzyme conjugate, there is no inhibition. Thus, the product can be used in a homogeneous enzyme. . .

DETD . . . added 200 .mu.l of a chilled DMF solution containing 44 .mu.M of NHS and 40 .mu.M of ECDI and the **mixture** allowed to stand 2 days at 4.degree. under argon.

DETD To the stirred **mixture** was added slowly in primarily 5 .mu.l increments the NHS ester prepared above with intervening additions of 1 N sodium. . .

DETD . . . solution saturated with argon for 40 min (5.5 ruby ball) and 50 .mu.l of the morphinethiol solution added slowly. The **mixture** was then stored under argon at 4.degree. for 30 days. At the end of this time, the **mixture** was transferred to a dialysis sack and dialyzed against 5.times.125 ml portions of 0.01 M phosphate, pH 7.0 for several. . .

DETD . . . was suspended in 100 ml of anhydrous methanol. Ammonia gas was introduced with stirring. The suspension became thinner and the **mixture** began to warm up. The **mixture** was cooled by ice bath and saturated with NH.sub.3 for one hour. After filtration the solid cake was treated once. . .

DETD . . . was packed with 500 g (60-200 mesh) of silica gel. The eluent is the lower phase of the following solvent **mixture**: $CHCl_3$ /isopropyl alcohol/17% NH_4OH in a ratio of 2/1/1.

DETD Five grams of gentamicin complex was dissolved in a **mixture** of methanol and chloroform. To this solution was added silica gel (5 g) and the **mixture** concentrated to a dry powder. The **mixture** was placed on the top of the column, wetted with solvent, topped with 2-3 cm of sand and covered with. . . Gentamicin C_1 collected pure at 5 l. to 5.65 l. weighed 610 mg. It followed a long fraction of a **mixture** of C_1 and C_2. Then 900 mg of gentamicin C_2 was collected. The pure C_{1a} isomer isolated was very small.

. .
DETD . . . methanol under argon and at room temperature. To this solution was added ethyl trifluoroacetate (1 mmol, 160 mg) and the **mixture** was stirred overnight. Analytical tlc (silica, CHCl.sub.3 /MeOH/conc. NH.sub.4 OH:10/10/3) showed approximately 60% reaction but further reaction did not improve. . .

DETD . . . mmol) was placed in a dropping funnel with a dry ice jacket and was added over an hour. The resulting **mixture** was stirred at room temperature for an additional hour. Concentration on a warm water bath and oil pump gave 1.6. . .

DETD . . . in five minutes. The reaction was vigorous with gasing after the addition of 1.5 ml of Et.sub.3 N. The reaction **mixture** was stirred at room temperature for two hours and then subjected to degasing under the water aspirator. To the resulting **mixture** was added 20 ml of water and the aqueous solution extracted with 50 ml of CH.sub.2 Cl.sub.2. The aqueous layer. . . with 50 ml of saturated NaHCO.sub.3. Upon acidification with 5 N H.sub.2 SO.sub.4 to pH 2 and extraction by a **mixture** of CH.sub.2 Cl.sub.2 --CHCl.sub.3 (total 120 ml), the product solution was washed with saturated brine and dried (MgSO.sub.4). Concentration of. . .

DETD . . . 2'-N-trifluoroacetylgentamicin C.sub.1 (0.19 mmol, 107 mg) in 8 ml of dry THF. The addition took 0.5 hour and the reaction **mixture** was allowed to proceed at room temperature overnight. The resulting **mixture** was concentrated and passed through a small silica gel column, first with 1:1 chloroform-hexane, then 10% MeOH in chloroform and. . .

DETD . . . (0.2 mM, 38 mg) were dissolved in 1 ml of anhydrous DMF in an ice bath under argon. The capped **mixture** was stirred in a cold room overnight. The tan colored solution was stored in the freezer ready for use.

DETD . . . under nitrogen was added slowly a solution of 0.08 g (0.5 mmol) of homocysteinthiolactone in 2 ml of THF. The **mixture** was then stirred at room temperature under nitrogen for 2 hrs and could then be used directly for conjugation to. . .

DETD . . . ml of triethylamine in 10 ml of methylene dichloride at 0.degree. was added 1.86 g (10 mmol) of 2,4-dinitrofluorobenzene. The **mixture** was then stirred at room temperature overnight and the volatiles removed in vacuo to leave a yellow residue. The residue. .

DETD . . . (1 mmol) of N-hydroxy succinimide. Under nitrogen at 0.degree. was then added 0.287 g (1.5 mmol) of ECDI and the **mixture** stirred at 0.degree. for 2 hrs followed by adding the **mixture** dropwise to a solution of 0.467 g (1 mmol) of tobramycin in a **mixture** of 12 ml water and 3 ml DMF. After stirring overnight at 0.degree., the solvent was removed in vacuo to. . .

DETD . . . a solution of 2.01 ml (0.024 mol) of bromoacetyl bromide in 10 ml of methylene dichloride. After the addition, the **mixture** was stirred for 3 hrs and poured into 1 N aqueous hydrochloride. The organic layer was separated and then washed successively with 1 N HCl, water and brine. After drying over anhydrous sodium sulfate, the

mixture was evaporated to dryness in vacuo to yield 6 g of a light brown product, which upon recrystallization from hexane-ethyl. . .

DETD . . . C. in an inert polar solvent. Illustrative solvents include tetrahydrofuran, dimethylformamide, ethyleneoxy and propyleneoxy ethers, and the like. The reaction **mixture** may then be worked up in conventional ways, the disulfide cleaved to provide a thio compound, which may then be. . .

L14 ANSWER 30 OF 45 USPATFULL

ACCESSION NUMBER:	82:11141 USPATFULL		
TITLE:	Novel ether substituted fluorescein polyamino acid compounds as fluorescers and quenchers		
INVENTOR(S):	Khanna, Pyare, Mountain View, CA, United States Ullman, Edwin F., Atherton, CA, United States		
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4318846		19820309
APPLICATION INFO.:	US 1979-73163		19790907 (6)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Schain, Howard E.		
LEGAL REPRESENTATIVE:	Rowland, Bertram I.		
NUMBER OF CLAIMS:	22		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1641		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . efficient response to such reagent. Furthermore, where the fluorescer is to be used in the presence of serum or other **composition**, which is in itself fluorescent, it is desirable that the fluorescer absorb energy in a substantially different range from that. . .

SUMM . . . swellable or non-swellable by aqueous media; the support may be cross-linked or non-cross-linked, may be a single substance or a **mixture** of substances; naturally occurring supports may include polysaccharides, nucleic acids, poly(amino acids) e.g. polypeptides and proteins, rubbers, lignin, vesicles, combinations. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium

Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazolyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . ml) and saturated NaCl solution (1.times.10 ml) and then evaporated to leave a solid which was crystallized from ethyl acetate-hexane **mixture** to provide the product as white silky needles (1.35 g). mp 69.degree.-70.degree..

DETD A **mixture** of the product of Example 1 (200 mg) and 100 mg of 1,2,4-benzenetricarboxylic anhydride was heated with 15 mg zinc chloride at 180.degree.-85.degree. for 30 min. The resulting red **mixture** was dissolved in 5% aqueous sodium hydroxide and precipitated with dilute HCl to pH 1. The precipitate was then chromatographed. . .

DETD A **mixture** of pyrogallol-2-methyl ether (4 g) and 1,2,4-benzene tricarboxylic anhydride (2.3 g) was heated in an open test tube in a. .

. spots were combined and the solvent removed to give a red residue which was macerated with 20 ml of a **mixture** of CCl.sub.4 :CH.sub.2 Cl.sub.2 (95:5). The resulting red solid (.sup..about. 1.1 g) was filtered and was a single spot on. . .

DETD . . . refluxed (outside bath temperature 80.degree.-85.degree.) for 1
hr under N.sub.2. TLC examination (CH.sub.2 Cl.sub.2 :methanol:acetic acid 85:14:1) of the refluxing **mixture** indicated the formation of monoiodinated and small amounts of diiodinated derivatives along with
starting material.

DETD . . . (500 mg) and NaHCO.sub.3 (250 mg) followed by 1 hr heating was repeated two more times. TLC of the final **mixture** indicated the presence of large amounts of diiodinated derivatives along with traces of monoiodinated derivative.

DETD . . . 25 ml of 20% fuming sulfuric acid was dissolved 10 g of 4-methylphthalic anhydride and 0.5 g powdered iodine. The **mixture** was heated at 90.degree.-100.degree. and chlorine gas was bubbled through the solution continuously. After heating for 24 hrs,
an additional. . . The solid was washed with 20 ml cold water and dried in vacuo. The product was believed to be a **mixture** of 3,5,6-trichloro-4-methylphthalic diacid and anhydride.

DETD . . . phosphate buffer, pH 8, was slowly added 0.7 mg of the above NHS ester in 25 .mu.l DMF and the **mixture** stirred for 1 hr at 0.degree.-5.degree. and then for an additional hour at room temperature.
The product was purified by. . .

DETD . . . vacuo to remove the last traces of solvent. The resulting deep red solid was stirred with 12 ml of benzene-hexane **mixture** (1:1) for 20 min and the resulting deep violet solid filtered. This solid was found by TLC in CH.sub.2 Cl.sub.2. . .

DETD . . . a reaction flask was introduced O.sup.2 -methyl pyrogallol (300
mg), succinic anhydride (100 mg) and ZnCl.sub.2 (20 mg) and the **mixture** heated at 180.degree.-85.degree. for 15 min. The product was purified by preparative TLC (CH.sub.2 Cl.sub.2 :MeOH:AcOH::90:10:0.5), and the purified product. . .

DETD . . . freshly prepared solution of cuprous cyanide [prepared from a solution of cuprous chloride and sodium cyanide[with vigorous stirring.
The **mixture** was allowed to come to room temperature and then stirred overnight. Next day, the benzene layer was separated and concentrated. . . nitrile. This was not purified but hydrolyzed directly to the amide. A solution of the nitrile (4.5 g) in a **mixture** of dioxane (30 ml) and 4% aq. NaOH (70 ml) was refluxed for 8 hrs. The solution was cooled, extracted. . .

DETD . . . in 1 ml of water); while maintaining the temperature of the solution below 30.degree.. After the addition was complete, the **mixture** was diluted with ice to give a white precipitate which was filtered and further purified by dissolving in 10% K.sub.2. . .

DETD . . . above prepared acid (0.56 g) was added alkaline KMnO.sub.4 (1.81 g in 10 ml of 10% K.sub.2 CO.sub.3) and the **mixture** heated at 110.degree. for 3 hrs. The resulting **mixture** was acidified with 6 N H.sub.2 SO.sub.4 to pH 1 and excess KMnO.sub.4 removed by treatment with oxalic acid. Extraction. . .

DETD Into a reaction flask was introduced 4-thiomethylresorcinol (200 mg), phthalic anhydride (104 mg) and zinc chloride (10 mg) and the **mixture** heated at 180.degree. for 5 min. The product was purified by preparative TLC using CH.sub.3 OH:CH.sub.2 Cl.sub.2 :HOAc (9:1:0.1) and. . .

DETD . . . of buffer with 25 .mu.l of the appropriately diluted product of
Example 6 in 250 .mu.l of buffer, incubate the **mixture** for 10

min, add 2 ml of the buffer and then determine the fluorescent signal. When the fluorescein-IgG conjugate was. . .

DETD The fluorescent signal from the morphine conjugate was plotted against the concentration of antimorphine conjugate. The assay **mixture** contained 8.75 ng/2.55 ml of the fluorescer-morphine conjugate. The antimorphine conjugate was added in amounts varying from 0 to 125 .mu.g, with varying ratios of quencher to antimorphine. The buffer employed for the assay **mixture** 0.01 M PO.sub.4.sup.3- 0.15 M NaCl and 2% PEG 6000. The fluorescein was measured with a Perkin-Elmer 1000 at a. .

DETD By adding morphine to the assay **mixture**, the fluorescence was enhanced, demonstrating the specificity of the quenching effect.

L14 ANSWER 31 OF 45 USPATFULL

ACCESSION NUMBER:	81:47741 USPATFULL
TITLE:	Charge effects in enzyme immunoassays
INVENTOR(S):	Gibbons, Ian, Menlo Park, CA, United States Rowley, Gerald L., Cupertino, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4287300		19810901	
APPLICATION INFO.:	US 1979-61099		19790726	(6)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Wiseman, Thomas G.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	15
EXEMPLARY CLAIM:	1,7
LINE COUNT:	1855

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . weight % of the total protein as the antibody of interest. When preparing reagents which involve reactions with the antibody **composition**, the presence of the large amount of contaminant must be taken into account.

SUMM . . . system label will frequently be added prior to the charged member. The two reagents may be provided as a single **composition** or as separate compositions, depending upon the nature of the protocol.

SUMM . . . member to the analyte and incubating for a sufficient time for the system to at least approach equilibrium. To the **mixture** may then be added the charged member and at the same time or immediately thereafter, any additional components of the. . .

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, a single or plurality of compounds which share at least one common. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. determinant or epitopic site. Illustrative receptors include. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or

portion, e.g by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . Where the signal label is a large molecule such as an enzyme, and one is dealing with a relatively impure **mixture** containing either the ligand or receptor, one will normally provide for a plurality of substituents on the signal label, to. . .

SUMM . . . of a member of the specific binding pair is to minimize background effects. That is, if one employed an impure **mixture** of receptor, for example, and conjugated it to enzyme, if there was a one to one mole ratio of molecules in the impure **mixture** to molecules of enzyme, a substantial proportion of the enzyme would only be bound to impurities and if active would. . .

DETD . . . 150797, 8.5 mg/ml) was centrifuged for 10 min and the precipitate dissolved in 3 ml PBS, N.sub.3 Mg. To the **mixture** was then added 0.3 ml 100 mM dithioerythritol and the **mixture** incubated for 1 hr at room temperature, followed by chromatographing on a 2.6.times.75 cm Biogel A5M (200-400 mesh) column equilibrated. . .

DETD . . . 35.3 mg/ml solution of the antiHIgG was added 60 .mu.l (10 mg/ml DMF) of m-maleimidobenzoic acid NHS ester and the **mixture** allowed to stand at room temperature for 30 min, followed by the addition of 0.18 ml of 1 M sodium acetate, pH 5. The reaction **mixture** was then dialyzed 2.times.500 ml (degassed) 20 mM sodium acetate, pH 5, 0.15 M NaCl for 1 hr at room. . . phosphate, pH 7, followed by 2 ml of the above reaction product at a concentration of 31.1 mg/ml and the **mixture** incubated at room temperature for 4 hrs. The reaction was terminated by the addition of 0.2 ml of 10 mM. . .

DETD . . . HIgG (35.3 mg protein/ml) was added 60 .mu.l of a 32 mM solution of m-maleimidobenzoic acid NHS ester and the **mixture** stirred at RT for 30 min. After adding 0.18 ml 1.0 M NaOAc, pH 5.0, the solution was dialyzed against. . . 0.2 ml of 0.5 M PO.sub.4, pH 7.0, followed by 2 ml of the above solution (31.1 .mu.g/ml) and the **mixture** incubated at RT for 4 hrs. The reaction was terminated by the addition of 0.2 ml 10 mM cysteine HCl. . .

DETD . . . 0.5 hr, 1 ml of a 1 M hydroxylamine-HCl adjusted to pH 8 with sodium hydroxide was added and the **mixture** incubated at room temperature for 30 min before dialyzing 5.times.0.5 l. PBS, N.sub.3, Mg

at room temperature overnight. The final. . .
DETD . . . 0.33.mu. mole) was added 25 .mu.l of a 50 mg/ml fluorescein isothiocyanate DMF solution (9.2 fluorescein/protein mole ratio) and the
mixture stirred at RT in the dark. The product was gel filtered on Sephadex G25M with PBS pH 6.8 N.sub.3, Mg,. . .
DETD . . . portion of silver oxide (20 g, 0.17 equiv.) was added. Stirring
was continued for an additional twenty minutes. The reaction **mixture** was filtered through a Celite pad to remove the silver salts. The filtrate was evaporated to give a crude brown. . .
DETD The tetraacetate IV (119 g, 0.226 mole) was added to methanol (1000 ml).
The **mixture** was heated at 60.degree. until the solid dissolved. Triethylamine (25 ml) was then added, and the solution was heated at. . .
DETD The reaction **mixture** was allowed to cool. Ethanol (1 l) was added slowly to the stirred reaction **mixture**. The dextran began to precipitate after 350 ml had been added. Additional ethanol (2 l) was added to ensure complete. . .
DETD . . . of buffer with 0.05 ml of the appropriate concentration of human IgG and 0.10 ml of buffer and incubating the **mixture** for 3 hrs at room temperature. To the **mixture** was then added 0.1 ml of the succinylated antibody and 0.25 ml of buffer followed immediately (15 secs) by the. . .
DETD . . . the enzyme conjugate (Ex 1D) with 50 .mu.l of HIgG in 0.2 ml buffer(PBS, N.sub.3, Mg, RSA) and incubating the **mixture** for 1 hr at RT. To the **mixture** was then added 100 .mu.l of the fluorescein labeled anti(HIgG) and 0.25 .mu.l buffer, the **mixture** incubated for 15 sec at RT and 100 .mu.l of 4 mM ONPG conjugated dextran (40,000 mw) in PBS, N.sub.3. . .
DETD In the next two assays, antienzyme was used as an inhibitor of enzyme which remains unbound to antigen. A **mixture** was prepared of 1.5 ml of the enzyme-antibody conjugate described previously and 1.5 ml of the succinylated antibody diluted 1:16. To 0.05 ml of the appropriate
human IgG solution was added 0.10 ml of the above **mixture** and either (1) 0.05 ml antienzyme added within a few minutes or (2) the **mixture** incubated followed by the addition of 0.05 ml of the antienzyme. In each case, the mixtures were then incubated for. . .
CLM What is claimed is:
7. A **composition** useful for the immunoassay of claim 1 comprising, a macromolecular charged substrate or coenzyme and modified members of a specific. . .
8. An assay **composition** according to claim 7, wherein said charged member is polycarboxyl substituted antiligand and said signal labeled member is .beta.-galactosidase substituted. . .
9. An assay **composition** according to claim 7, wherein said macromolecular charged substrate is a positively charged substrate for said .beta.-galactosidase having a plurality. . .
10. An assay **composition** according to claim 7, wherein said charged member is a polyphenolic substituted antiligand and said signal labeled member is .beta.-galactosidase. . .
11. An assay **composition** according to claim 10, wherein said charged macromolecular substrate is a positively charged substrate for said .beta.-galactosidase having a plurality. . .

L14 ANSWER 32 OF 45 USPATFULL
ACCESSION NUMBER: 81:40928 USPATFULL
TITLE: Double antibody for enhanced sensitivity in immunoassay

INVENTOR(S):	Zuk, Robert F., San Francisco, CA, United States Gibbons, Ian, Menlo Park, CA, United States Rowley, Gerald L., Cupertino, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4281061		19810728	
APPLICATION INFO.:	US 1979-61542		19790727	(6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wiseman, Thomas G.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 1497
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Method and **composition** are provided for determining small amounts of organic compounds in a wide variety of media by employing an organic receptor. . .

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic (antigenic determinants) or haptenic, a single or. . .

SUMM Receptor--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. hemophilus
H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis

Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Actinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .
SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .
SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.
SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.
SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.
DETD . . . a 0.07 M solution in acetone with rapid stirring at RT and the stirring continued for 30 min. To the **mixture** was then added hydroxylamine-HCl in water (0.75 M, adjusted to pH 8.0, with NaOH) to a final concentration of 0.25 M. After standing at RT for 30 min, the **mixture** was then dialyzed 5.times.0.5 l. of 50 mM phosphate, pH 7.0. The product was found to have 8.2 succinyl residues. . .
DETD . . . phosphate buffer, pH 7.0, was dissolved 33 mg of HIgG to provide a final concentration of 5 mg/ml. To the **mixture** was added with stirring 6.4 mmoles of MBSE as a 10 mg/ml solution in dry DMF with stirring under nitrogen.. . .
DETD . . . portion of silver oxide (20 g, 0.17 equiv.) was added. Stirring was continued for an additional twenty minutes. The reaction **mixture** was filtered through a Celite pad to remove the silver salts. The filtrate was evaporated to give a crude brown. . .
DETD C. The tetracetate prepared above (B) (119 g, 0.226 mole) was added to methanol 1 l. The **mixture** was heated at 60.degree. until the solid dissolved. Triethylamine (25 ml) was then added, and the solution was heated at. . .
DETD The reaction **mixture** was allowed to cool. Ethanol (1 l.) was added slowly to the stirred reaction **mixture**. The dextran began to precipitate after 350 ml had been added. Additional ethanol (2 l.) was added to ensure complete. . .
DETD . . . .mu.l aliquots combined with 50 .mu.l aliquots of the enzyme conjugate and incubated for 1 hr at RT. To the **mixture** was then added 25 .mu.l of serial dilutions of goat antibody to the antiHIgG (2.4 mg/ml) in the same buffer and the **mixture** incubated for an additional hour. The assay was then performed as follows. The dextran

linked galactosidyl ether was dissolved in. . . a total volume of 1 ml. Absorption was read at 420 nm employing a Stasar Spectrophotometer at 37.degree. with the **mixture** aspirated into the Spectrophotometer and readings taken at 10 and 40 sec. The activity is expressed as a rate (.DELTA.OD/min.).. . .

DETD . . . mg/ml) was mixed with 25 .mu.l. of a serially diluted solution of rabbit antiHIgG in the same buffer and the **mixture** incubated for 1 hr at RT. To the **mixture** was then added Conjugate 2 of Example 3 in 50 .mu.l (9 .mu.g/ml .beta.-galactosidase) and incubation continued for a further hour. To the **mixture** was then added goat anti(rabbit antiHIgG) (14.9 mg/ml) in 25 .mu.l. and the **mixture** incubated for a third hour followed by assay with ONPG conjugate to Dextran of 40,000 m.w. The following table indicates. . .

DETD . . . 0.5 ml PBS, 2% PEG 6000, 0.05% NaN.sub.3, pH7.8 buffer was added rabbit(antiHIgG) (20 .mu.l, 9.1 mg protein/ml) and the **mixture** incubated at room temperature for 0.5 hr, followed by the addition of anti(rabbit(HIgG)) (Miles, Cat. No. 65-159, Lot S404, IgG. . .

CLM What is claimed is:

15. An assay **composition** for use in the method of claim 1 comprising in combination in relative predetermined amounts to substantially optimize the signal. . .

16. An assay **composition** according to claim 15, wherein labeled ligand is enzyme bonded to ligand and said macromolecular member is an enzyme substrate.

. . .

17. An assay **composition** according to claim 15, wherein labeled ligand is fluorescer bonded to ligand and said macromolecular member is antifluorescer.

L14 ANSWER 33 OF 45 USPATFULL

ACCESSION NUMBER:	81:34595 USPATFULL
TITLE:	Macromolecular environment control in specific receptor assays
INVENTOR(S):	Litman, David J., Palo Alto, CA, United States Harel, Zvi, Stanford, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4275149		19810623	
APPLICATION INFO.:	US 1978-964099		19781124	(5)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Wiseman, Thomas G.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	46
EXEMPLARY CLAIM:	1,19,46
LINE COUNT:	2543

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of

recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . tulareusis

Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . and washed in 1 mM HCl, 200 ml) in 0.1 M sodium bicarbonate, pH 8.1, 0.5 M NaCl and the **mixture** stirred at 40.degree. for six hours, followed by stirring for two hours at room temperature. To the solution was then. . . added 0.25 ml of 1 M 2-aminopropanol, pH 8.0 and the reaction allowed to stir overnight at 4.degree.. The reaction **mixture** was then washed by centrifugation 3.times.2 ml 0.1 M borate, pH 8.5, 1 M NaCl, followed by 2.times.2 ml of. . .

DETD . . . and 50 .mu.l of a 10 mg/ml solution (added in 25 .mu.l aliquots) of meta-maleimidobenzoic acid NHS ester and the

mixture stirred for 30 min at room temperature. The reaction **mixture** was then chromatographed on a 2.5.times.25 cm G50 column equilibrated with N.sub.2 purged 0.1 M phosphate, pH 6, 10 mM. . .

10 mM EDTA containing 13.5 mg HK, was added 50 .mu.l 2 M glucose and 0.4 ml DMF and the **mixture** stirred under nitrogen at room temperature. To the solution was added 100 .mu.l in four aliquots of a 20 mg/ml. . . for reaction to occur, 0.4 ml of 1 M hydroxylamine, pH 7.5, was added with stirring under nitrogen and the **mixture** stirred for 60 min at room temperature.

DETD The reaction **mixture** was then chromatographed on a 2.5.times.25 cm G50 column in 0.1 M phosphate, pH 6, 10 mM EDTA, nitrogen purged,. . . mg), the aqueous medium being 0.1 M phosphate, pH 6, 10 mM EDTA, 30 mM glucose, and nitrogen purged. The **mixture** was allowed to react at 4.degree. for 48 hrs.

DETD The reaction **mixture** was then chromatographed on a BiogelA5M column in 0.1 M phosphate, pH 7, 10 mM EDTA, 2 mM .beta.-Me 0.02% azide, the column nitrogen purged, and the **mixture** applied to the column in 6 ml and eluted in 3.5 ml fractions. Fractions 45 to 68 were pooled and. . .

DETD . . . 155 .mu.l of 2 M hydroxylamine HCl pH 8.0 were added. After stirring for an additional 2 hrs, the reaction **mixture** was dialyzed at 4.degree. against 350 ml of 0.05 M sodium phosphate buffer pH 7.0 over 72 hrs with six. . .

DETD . . . 1.0 M hydroxylamine HCl pH 7.5 was added and the stirring was continued for an additional 10 min. The reaction **mixture** was chromatographed on 0.9.times.10.5 cm G-25 fine Sephadex column (degassed and saturated with argon) with 0.05 M sodium phosphate buffer,. . .

DETD . . . stirring, the reaction was terminated by addition of 0.4 ml of 1 M sodium acetate buffer pH 5.0. The reaction **mixture** was chromatographed on 0.9.times.25 cm G-25 fine Sephadex column with 0.02 M sodium acetate buffer, pH 5.0; fractions of 1.0. . .

DETD . . . under nitrogen and the RIgG-SH solution (Example 4) was added slowly. The pH was brought to 6.7 and the reaction **mixture** was stirred at r.t. for 3 hrs and overnight at 4.degree.. After addition of 0.2 ml 0.02 M mercaptoethanol solution and stirring at r.t. for 30 min, the reaction **mixture** was kept over 72 hrs. at 4.degree.. The solution was concentrated to 1 ml volume in Amicon through PM30 Diaflo.RTM.. . .

DETD . . . and 12 ml chlorotrimethylsilane were stirred in 80 ml dry pyridine overnight at r.t. under an argon atmosphere. The reaction **mixture** was evaporated to dryness under reduced pressure, ether was added and the white crystals were removed by filtration. The supernatant. . .

DETD . . . stirred at r.t. for 60 hrs. Water (26 ml) was added and the solution was stirred for 30 min. The **mixture** was evaporated to dryness, 750 ml of methanol, 130 ml of water and 5.3 ml of acetic acid were added and the **mixture** was stirred overnight. The precipitate was filtered and the methanol was evaporated under reduced pressure to give 8 g of. . .

DETD A reaction **mixture** was prepared by combining 4 ml HIgG (8.34 mg/ml, 50 mM phosphate buffer, pH 7.0), 2.17 ml phosphate buffer, pH. . at room temperature to the reaction was added 1 ml 1 M NaOAc to adjust the pH to 5. The **mixture** was then chromatographed on Sephadex G25-F (2.4.times.20 cm), eluted with 20 mM NaOAc, pH 5.0,

containing 0.15 M NaCl at. . .

DETD . . . anti(HIgG) in 0.1 M NaHCO.sub.3, pH 8.1, 0.5 M NaCl and 0.9 g CNBr activated Sepharose 4B heads and the **mixture** stirred at 4.degree. for 6 hrs, followed by stirring at R.T. for 2 hrs. To the **mixture** was then added 0.1 volume 1 M 2-aminopropanol, pH 8.0 and the **mixture** stirred overnight at 4.degree.. By employing radioactive Ranti(HIgG), it was found that 6.6 mg had coupled.

DETD . . . was added 2 g dextran T2000 (Pharmacia), followed by the addition of 10 ml 2.5 M aq. NaOH, and the **mixture** heated at 70.degree.-75.degree. for 1.5 hr and allowed to stand overnight. To the **mixture** was added 2 ml glac. HOAc and the **mixture** then dialyzed against 10 l 5% aq. HOAc (4.times.24 hr) and then against deionized H.sub.2 O, 10 l, (4.times.24 hrs).. . .

DETD . . . N,N'-bis-(3-aminopropyl)piperazine and 18 g (90 mmole) EDCI and

the solution allowed to stand at R.T. for 24 hrs. The reaction **mixture** was then dialyzed against 12 l. deionized water containing 150 g K.sub.2 HPO.sub.4 and 75 g KH.sub.2 PO.sub.4 (4.times.24 hrs). . .

DETD c. To 10 ml DMF was added 387 mg 2-nitro-5-carboxyphenyl-.beta.-galactoside, 249 mg EDCI and 151 mg N-hydroxy sucnimide and the **mixture** stirred at R.T. for 1 hr. To 10 ml of aqueous solution containing the aminosubstituted dextran prepared above (9.2 mM in amino groups) was added 2.5 ml of the NHS ester prepared above and the reaction **mixture** stored at R.T. for 24 hrs. The reaction **mixture** was dialyzed against water (4.times.) and the product assayed for o-nitrophenyl-.beta.-galactoside groups (ONPG). The product was found to be 7.0. . .

DETD . . . .mu.l of beads is added to 50 .mu.l of incubation buffer containing varying amounts of human IgG. To the incubation **mixture** is added 8 .mu.l of the rabbit anti(HIgG)-HK conjugate and the samples incubated for 30 min at 37.degree.. To the **mixture** is then added 1 ml of assay buffer, the sample vortexed for approximately 3 sec and immediately aspirated into a. . .

DETD . . . Mg is added to a final volume of 1.05 ml which is promptly aspirated into a spectrophotometer cell. The reaction **mixture** is then read at 37.degree. at 420 nm by taking readings at 10 and 40 sec

after addition of the. . .

DETD . . . in that order. Incubate at R.T. for 3 hrs. Add 0.1 ml substrate

and 0.4 ml buffer and aspirate the **mixture** into a spectrophotometer cell and read at 37.degree. at 10 and 40 sec after adding the substrate. The following table. . .

CLM What is claimed is:

46. A **composition** comprising a discrete porous particle of a size in the range of about 500 nm to 100.mu. to which is. . .

L14 ANSWER 34 OF 45 USPATFULL

ACCESSION NUMBER:	81:31786 USPATFULL		
TITLE:	Purification of reagents by disulfide immobilization		
INVENTOR(S):	Schwarzberg, Moshe, Hastings on Hudson, NY, United States		
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4272506		19810609
APPLICATION INFO.:	US 1979-71526		19790831 (6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Fagelson, Anna P.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1,9
LINE COUNT: 1010
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . cleavable under mild conditions to provide a binding pair member-support conjugate. Combining the binding pair member-support conjugate with a labeled **composition** containing the reciprocal member of the binding pair, so that the labeled reciprocal member becomes bound to the support through. . . to provide labeled reagent for immunoassays. In particular, an antibody is linked to a support by disulfide linkage and a **composition** containing the reciprocal antigen to the antibody is labeled with a chromophore, particularly fluorescer. The support is freed of labeled. . .

SUMM . . . mercapto groups with a functionality which allows for reaction with a second mercapto group to produce a disulfide linkage. A **composition** containing one of the members of a specific binding pair--antigen and its homologous antibody--is modified to introduce mercapto groups, if such mercapto groups are not naturally present. The mercapto group containing **composition** is combined with the activated support to provide for the binding of the member of a specific binding pair to the support through disulfide links. A second **composition** having the reciprocal member of the specific binding pair is labeled with labels capable of providing a detectible signal, the labels being in sufficient amount to ultimately insure a desired signal level. The labeled **composition** is then combined with the support **composition**, where the binding pair members bind, so that the labeled member is now bound to the support through the intermediary. . .

SUMM . . . member of the specific binding pair, which is labeled with an appropriate label, and is generally part of a complex **mixture**, is combined with the reciprocal member bound to the support, so as to produce the immunological pair member complex. The. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM . . . H. aegypticus
H. parainfluenzae
Bordetella pertussis
Pasteurellae
Pasteurella pestis
Pasteurella tulareusis
Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens

Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium bovis
Mycobacterium avium
Mycobacterium leprae
Mycobacterium paratuberculosis
Antinomycetes (fungus-like bacteria)
Actinomyces israelii
Actinomyces bovis
Actinomyces naeslundii
Nocardia asteroides
Nocardia. . .

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steriod alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their matabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procainemide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . M NH.sub.2 OH at pH 7.4 (freshly prepared) was added and stirred for 5 min. The pH of the reaction **mixture** was reduced to 5.2 by the addition of solid L-malic acid and immediately applied for separation on Sephadex G-25 (0.9.times.25. . .

DETD . . . were degassed and saturated with argon before use.) To the packed gel a solution of DTNB was added and the **mixture** shaken for 20 min. at room temperature (DTNB solution-dissolve 8 mg of DTNB in 0.3 ml methanol, add 3 ml. . .

DETD . . . ml) was mixed with 2 ml of Thiol labeled antibody and 2 ml potassium phosphate buffer. The pH of the **mixture** was adjusted to 8.0 by the addition of Tris base. After 36 hrs. the gel was washed with potassium phosphate. . .

DETD . . . fraction III (Miles) for 30 min. in 300 ml 0.05 M Sodium phosphate-0.2 M sodium chloride buffer, pH 8.0. The **mixture** was centrifuged to remove undissolved protein and the supernatant was dialyzed against 3 changes of deionized water over 3 days.. . . The protein was labeled with FITC (8.0 mg in 0.5 ml dry DMF) for 3 hrs. at room temperature. The **mixture** was separated on Sephadex G-25 (0.9.times.25 cm) equilibrated with 0.05 M KPO.sub.4 buffer containing 2 mM EDTA at pH 8.0. Since the capacity of the column was small,

separation was done in two portions (2.4 ml of reaction **mixture** each). The collected conjugate, 8.5 ml, had 24.6 mg/ml protein estimated by UV (E.sup.1% =14), about 2.6 mg/ml IgA estimated. . .

DETD . . . one hundred ml of sheep anti-human IgA was added 250 mg of IgG (Cohn fraction II, Miles Lab.) and the **mixture** stirred overnight in the cold. The resulting precipitate was removed by centrifugation. To the supernatant was added 50 ml saturated. . .

DETD . . . as follows. The assay buffer is 0.01 M PBS (0.15 M NaCl) plus 2% PEG 6000, pH 8.0. An assay **mixture** is prepared as follows. Into a vial is introduced 25 .mu.l of the sample or buffer+250 .mu.l buffer, followed by 25 .mu.l of the fluorescent reagent+250 .mu.l buffer+25 .mu.l of the quencher reagent+250 .mu.l buffer, the **mixture** vortexed for 2-3 sec. followed by a 10 min. incubation at RT. The **mixture** is then diluted with 2 ml buffer and vortexed 2-3 sec. The fluorescent working solution was fraction 2, Ex. 6. . .

DETD . . . in 50 .mu.l dry DMF was added from a syringe while stirring. The addition took about 0.5 min. and the **mixture** stirred for an additional 3 min. Then 0.4 ml of 1 M NH.sub.2 OH solution at pH 7-7.3 (obtained by neutralization 1 M NH.sub.2 OH.HCl with 10 N NaOH) freshly prepared was added and the **mixture** stirred for another 3 min. The pH was lowered to 5.0 by the addition of solid citric acid and the reaction **mixture** dialyzed for 8 hrs. against 2 l of 0.1 M KH.sub.2 PO.sub.4 (2 mM EDTA) which was degassed and saturated. . .

DETD . . . 1 M NH.sub.2 OH (pH 7-8) was added and stirred for an additional 3 min. The pH of the reaction **mixture** was then dropped to 5.0 by the addition of solid citric acid and immediately taken for dialysis. This was done. . .

DETD . . . 10 hrs. of dialysis was added to the activated gel, followed by H.sub.2 O (8-10 ml) until stirring of the **mixture** became possible. The pH of the **mixture** was adjusted to 8.0 by the addition of solid Tris base. The **mixture** was stirred very slowly overnight. Then it was packed in a column (0.9 cm diameter), and the buffer was eluted. . .

DETD . . . protein was labelled with 4 mg of FITC at pH9.0 as previously described. After 2 hrs at room temperature the **mixture** was separated on Sephadex G-25 equilibrated with PMS-containing buffer at pH8.0. The resultant conjugate, 13.2 ml gave OD.sub.276 =29.8, OD.sub.496. . .

CLM What is claimed is:

. . . labeled poly(amino acid) ligands for use in immunoassays, where the poly(amino acid) ligands which are labeled are present in a **mixture** and said labeled poly(amino acid) ligands are prepared by covalently labeling said **mixture** of compounds which includes said poly(amino acid) ligands, wherein said ligand is a member of a specific binding pair consisting. . . and its reciprocal antiligand and said labeled poly(amino acid) ligand is substantially enriched relative to other labeled compounds in said **mixture**; said method comprising: affixing to a displaceable disulfide substituted support a mercapto substituted member of said specific binding pair by. . . disulfide linkage; binding to said affixed specific binding pair member labeled reciprocal member of said specific binding pair from a **mixture** of other labeled material; removing from said support non-specifically bound label; and cleaving said disulfide to obtain a labeled reagent. . .

. . . method for preparing fluorescer-labeled poly(amino acid) ligands for

use in immunoassays, where the poly(amino acid) ligands are present in a **mixture** and said fluorescer-labeled poly(amino acid) ligands are prepared by covalently fluorescer labeling said **mixture** including said poly(amino acid) ligands wherein said labeled poly(amino acid) is substantially enriched relative to fluorescer label bound to other than said ligand in said **mixture**; said method comprising: displacing an aryl disulfide substituted support with mercapto containing antiligand for said poly(amino acid) ligand to form an antiligand disulfide substituted support; binding fluorescer labeled ligand from a **mixture** of other labeled material to said antiligand on said support; removing from said support fluorescer label other than bound to. . .

L14 ANSWER 35 OF 45 USPATFULL

ACCESSION NUMBER:	81:20553 USPATFULL
TITLE:	Fluorescence quenching with immunological pairs in immunoassays
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Schwarzberg, Moshe, Palo Alto, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4261968		19810414	
APPLICATION INFO.:	US 1979-37802		19790510	(6)
DISCLAIMER DATE:	19961113			
RELATED APPLN. INFO.:	Division of Ser. No. US 1976-731255, filed on 12 Oct 1976, now patented, Pat. No. US 4174383 which is a continuation of Ser. No. US 1975-591386, filed on 30 Jun 1975, now patented, Pat. No. US 3996345 which is a continuation-in-part of Ser. No. US 1974-497167, filed on 12 Aug 1974, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Fagelson, Anna P.			
LEGAL REPRESENTATIVE:	Rowland, Bertram I.			
NUMBER OF CLAIMS:	4			
EXEMPLARY CLAIM:	1			
LINE COUNT:	1664			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . to a hub molecule, usually a polymer, in combination with antibody bound to the other of the F-Q pair. The **composition** is irradiated with light at a wavelength, absorbed by the fluorescing molecule and the amount of fluorescence determined. By employing. . .

SUMM One chromophore is introduced into the assay medium covalently bonded to a receptor **composition** which specifically binds to the ligand. The second chromophore can be introduced into the assay medium in different ways: (1) covalently bonded to a receptor **composition** which is the same or different from the receptor **composition** conjugated to the first chromophore, but in both instances specifically binds to the ligand, and in the presence or absence of polyligand; or covalently bonded to ligand analog, where the ligand analog can compete with ligand for the receptor **composition**. The choice of modes of introduction will depend to a significant degree on the number of independent epitopic or haptenic. . .

DETD . . . fluorescer molecule, by accepting the energy which would otherwise be emitted as fluorescent light. As far as the molecule or

composition to which the chromophores are joined, in most instances, the fluorescer and quencher will be interchangeable, although there will frequently. . .

DETD Receptor **composition**--receptor **composition** is a homogeneous or heterogeneous **composition** capable of specific non-covalent binding to ligand and ligand analog and includes anti-ligand (a **composition** which specifically recognizes the ligand) and a combination of anti-ligand and anti(anti-ligand) (a **composition** which specifically recognizes the anti-ligand).

DETD . . . on the employment of two chromophores which form a fluorescer-quencher pair. One of the chromophores is covalently bonded to a **composition** (receptor) which specifically recognizes or binds to a ligand. The other chromophore is covalently bonded to ligand analog or receptor.. . .

DETD . . . the assay medium: ligand analog-chromophore, poly(ligand analog)-poly(chromophore), poly(ligand analog), one or two receptors and one or two receptor-chromophores. The first **composition** to be considered will be the ligand analog-chromophore.

DETD . . . should also be noted that when antibodies are prepared for a ligand having a plurality of epitopic sites, the receptor **composition** is not homogeneous. That is, the receptor will have antibodies which recognize different epitopic sites. In referring to receptor, it. . .

DETD . . . the nucleus molecule be water soluble, in most instances, it will be desirable. In any event, the nucleus molecule or **composition** will be capable of stable dispersion in an aqueous medium. Secondly, the nucleus molecule should not absorb light at the. . .

DETD The next group of alkaloids are the **cocaine** alkaloids, which includes, particularly as metabolites, benzoyl ecgonine and ecgonine.

DETD The alkaloids of primary interest are those which come within the category of drugs of abuse, such as morphine, **cocaine**, mescaline, and lysergic acid, which may be analyzed for the compound or its metabolite, depending on the physiological fluid which. . .

DETD Drugs of interest because of their physiological properties are those which are referred to as catecholamines. Among the catecholamines are **epinephrine**, ephedrine, L-dopa, and norepinephrine.

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD Clostridium **botulinum**

DETD . . . In this manner, the ratio of the two common receptors can be carefully controlled and accurately added to the assay **mixture**. The **mixture** can be a dry lyophilized **mixture** or an aqueous, normally buffered (pH 5-10; usually 6.5-8.5) solution of any desired concentration.

DETD . . . a matter of operability, but rather expedience. In most cases, the receptor is antibody, which will be a complex protein **mixture**, containing antibody for the ligand, as well as other antibodies and proteins. When the antibody **composition** is labeled with chromophore, a substantial proportion of the chromophore will be bound to protein other than the antibody for. . .

DETD . . . the two conjugated antibodies are combined with the unknown to be assayed, incubated, and the poly(ligand analog) added and the **mixture** further incubated. The times and temperatures previously indicated are also applicable in this assay.

DETD . . . chromophore, particularly quencher, is conjugated to

anti(anti-ligand) to provide anti(anti-ligand)-chromophore, which is employed in conjunction with anti-ligand as a receptor **composition** for ligand. In this manner, one can bind a larger number of quencher molecules to the ligand, enhancing the opportunity. . .

DETD B. O.sup.3 -aminoethylmorphine (100 mg) is dissolved in 5 ml of acetone and added to a **mixture** of acetone (20 ml), water (5 ml), and triethylamine (0.07 ml). To this solution is added a solution of FITC. . . with stirring during 15 min. Stirring is continued for an additional 80 min. while adjusting the pH of the reaction **mixture** to 9.5 with drops of dilute triethylamine solution in acetone (1.4 ml/10 ml acetone). The acetone is then partially removed. . .

DETD . . . O.sup.3 -carboxymethylmorphine and isobutyl chloroformate (0.1 mmole, large excess) in DMF (2 ml) added in the cold (0.degree.), and the **mixture** allowed to react for 3 hours. The gel was filtered and washed successively with H.sub.2 O (500 ml), 0.1 M. . .

DETD . . . and then stays stable, and is maintained at 9.0-9.5 if necessary, by careful addition of crystalline potassium carbonate. The reaction **mixture** is then applied to a Sephadex G-25(M) column (1.times.15 cm) with 0.01 M phosphate buffer pH 7.5 and elution of. . .

DETD . . . pH 9.5 with crystalline Na.sub.2 CO.sub.3. TRITC (0.5 mg) in acetone (20-30 .mu.l) was added at room temperature and the **mixture** stirred for 3 hrs. A precipitate formed which was removed by centrifugation and discarded. The conjugate was then separated twice. . .

DETD . . . of morphine (5-10 .mu.l of the standard morphine solutions) for one hour. FLUMO'S' (10 .mu.l) was then added and the **mixture** incubated for an additional one hour. The final volume of each tube was 3 ml. The final concentration of FLUMO'S'. . .

DETD . . . 1.5.times.10.sup.-6 M bovine gamma-globulin (390-430 .mu.l) Codeine in increasing concentrations (1.5.times.10.sup.-3 -1.5.times.10.sup.-6 M) is then added (10-40 .mu.l) and the **mixture** incubated at room temperature for 0.5 hr. To each of the tubes is then added 10 .mu.l (0.24 .mu.g) of. . .

DETD . . . bonded to a chromophore and antibody employed which is conjugated to the other member of the fluorescer-quencher pair or the **mixture** of antibodies indicated above employed. The assay is relatively rapid, and depending upon the concentrations, various incubation times are required.. . .

L14 ANSWER 36 OF 45 USPATFULL

ACCESSION NUMBER:	81:15079 USPATFULL
TITLE:	Fluorescent scavenger particle immunoassay
INVENTOR(S):	Zuk, Robert F., Mountain View, CA, United States Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4256834		19810317	
APPLICATION INFO.:	US 1979-28640		19790409	(6)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Wiseman, Thomas G.			
LEGAL REPRESENTATIVE:	Rowland, Bertram I.			
NUMBER OF CLAIMS:	23			

EXEMPLARY CLAIM: 1,8,10
LINE COUNT: 1746
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and in some instances impossible. Furthermore, where the antiligand is an antibody, the antibody is normally isolated as a complex **mixture** of globulins, of which a portion, usually less than 50%, is the antibody of interest. Where one is labeling the. . .

SUMM . . . normally required to label either the ligand or its homologous receptor. The homologous receptor, particularly when antibody, is normally a **mixture** of specific and non-specific immunoglobulins. With many antigens, the low concentrations of the antigens make their purification or concentration tedious, inefficient and expensive. Therefore, frequently, when labeling a member of the specific binding pair, one labels the impure **mixture**.

SUMM Labeling of the impure **mixture** creates a number of problems. One problem is that there will be a substantial amount of adventitious label unrelated to. . .

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand, which is mono or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor (antiligand)--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. determinant or epitopic site. Illustrative receptors include. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites.

SUMM The next group of drugs is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes ephedrine, L-dopa, **epinephrine**, narceine, papverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM . . . be adsorptive or non-adsorptive to proteins; the particles may be naturally occurring, synthetic or combinations thereof, a single material or **mixture** of materials, and are normally chemically inert, absorb light in the wavelength range of interest and are frequently black. Illustrative. . .

DETD Into 2 ml water was dispersed 50 mg activated charcoal and the **mixture** sonicated with a Branson Cell Disruptor, Model 35, cup horn, 50% pulse, setting 5, for 2 minutes. A total of 10 mg of an antifluorescein **composition** was diluted to 3 ml with PBS pH7.8 (0.05% NaN.sub.3) followed by the addition of 40 .mu.l of .sup.14 C. . . ml aquasol, 5746 cpm/100 .mu.l). The 3 ml of the antifluorescein was

combined with the sonciated charcoal dispersion and the **mixture** stirred overnight at r.t.

DETD The **mixture** was then centrifuged, 0.5 ml was taken from the supernatant, the pellet washed 5.times. with PBS pH7.8, (0.05% NaN.sub.3) a. . .

DETD . . . dialyzed against 0.1 M sodium carbonate, pH9.0, was added 0.2 mg of fluoresceinisothiocyanate in 50 ml of DMF and the **mixture** stirred at RT for 3 hrs. The **mixture** was then chromatographed on a Sephadex G-25 column in PBS, pH7.0. The product was isolated in a solution having 3.2. . .

DETD . . . against 0.1 M sodium carbonate, pH9.0) was added 10 .mu.l of 0.1 mg fluoresceinisothiocyanate in 100 .mu.l DMF and the **mixture** stirred at RT for 1 hr in the dark. The reaction **mixture** was then chromatographed on a Sephadex G-25 column in PBS, pH7.0. The product had a concentration of 4.95 mg/ml with. . .

DETD . . . carbonate was added 150 l of a solution of CNBr in acetonitrile at a concentration of 2 g/ml and the **mixture** stirred for 2.5 min. The beads were isolated and then washed with 0.1 M sodium carbonate, pH9.1, water and 0.1. . . sodium carbonate, pH9.1. To the beads were then added 2.9 ml of a HulgG solution (5.6 mg/ml) and the resulting **mixture** agitated overnight at 4.degree.. To the **mixture** was then added 0.5 ml of 1 M aminopropanol, pH8.0, and the **mixture** agitated for 1 hr at 4.degree.. The resulting beads were then washed three times each with a first aqueous solution. . .

DETD . . . .mu.l of HulgG-Sepharose CL6B (diluted 1:3) and 100 .mu.l of buffer were combined, incubated for 1 hr at RT, the **mixture** spun down and the pellet resulting from the beads washed with buffer. Approximately 50 .mu.l of the bead pellet (5.times.10.sup.-9. . . (CL6B) was combined with 650 .mu.l of buffer and 50 .mu.l of charcoal or 50 .mu.l of buffer, and the **mixture** incubated for 0.5 hr at RT. Setting the fluorescence obtained with a combination of fluorescein-anti-HulgG and HulgG-Sepharose CL6B at 100%. . .

L14 ANSWER 37 OF 45 USPATFULL

ACCESSION NUMBER:	80:56609 USPATFULL
TITLE:	Reagents and method employing channeling
INVENTOR(S):	Maggio, Edward T., Redwood City, CA, United States Wife, Richard L., Sittingbourne, England Ullman, Edwin F., Atherton, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4233402		19801111	
APPLICATION INFO.:	US 1978-893650		19780405	(5)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Warden, Robert J.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	44
EXEMPLARY CLAIM:	1
LINE COUNT:	1842

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte--The compound or **composition** to be measured, which may be a ligand which is mono-or polyepitopic, antigenic or haptenic, a single or plurality of. . .

SUMM Receptor--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occuring. . .

SUMM . . . covalently joined to a polyfunctionalized hub nucleus, either water soluble or insoluble, the hub nucleus having been indicated previously. This **composition** will be referred to as poly(ligand analog)--polylabel. Desirably, when receptor is bound to ligand in a complex, it will not. . .

SUMM . . . binding site. There can be a plurality of receptors and/or labels bonded together, particularly through a hub nucleus. Such a **composition** will be referred to as polyreceptor-polylabel. Desirably, when ligand is bound to receptor in a complex, there will not be. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitripytline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propranolol, griseofulvin, valproic acid, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Another situation is where a **composition** is introduced into the solution which acts as an inhibitor or quencher of the emission of light, either by fluorescence. . .

SUMM . . . evident from the discussion concerned with the reactant label, the signal producing label will vary widely as to its chemical **composition**, function, and nature of interaction with the signal mediator. As with the reactant label, it is desirable that the signal. . .

DETD . . . prepared phosphate buffer (0.3 M,pH 8.1) was dissolved 12.3 ml of HRP and 0.25 ml of FDNB added and the **mixture** allowed to stand for one hour. After withdrawing about 1 ml, 1.2 ml of 0.04 M periodate was added to the remaining 1 ml and the **mixture** stirred for about 0.5 hr at room temperature. To the **mixture** was then added 1.2 ml of ethylene glycol. The **mixture** was then dialyzed against buffer. To the residue in the dialysis bag was added 600 ml of goat anti(hIgG) (Miles Laboratories) and the **mixture** stirred for 3 hrs at room temperature. To the **mixture** was then added 9 mg sodium borohydride and the resulting reaction **mixture** allowed to stand at 4.degree. overnight with stirring. The reaction **mixture** was then dialyzed against PBS, followed by chromatographing on a Sephadex G200 column employing PBS, pH 7.2 as eluant. The. . .

DETD . . . GO, followed by the addition of 1 ml of 0.04 M sodium periodate. After one hr at room temperature, the **mixture** was diluted to 10 ml and concentrated on Diaflo Ultrafilter to 1 ml. To the

mixture was added 3 ml sodium borohydride and after standing overnight, 10 ml of PBS pH7 was added. After concentrating to 1 ml with a Diaflo Ultrafilter the **mixture** was chromatographed on a 0.3.times.45 cm Sephadex G200 column. Employing PBS pH7.2 buffer as an eluant, the fractions were monitored. . .

DETD . . . the following experiments were carried out. A plurality of tubes of different concentrations were prepared. The following table indicates the **composition** of the reaction media.

DETD The total volume for all the tubes is 25 ml. The materials were added in the order indicated and the **mixture** incubated for 34 min at room temperature prior to addition of the G/L solution. Readings were then taken at a. . .

DETD . . . or antiligand can only be obtained in relatively impure form, one can diminish the background effect when labelling the impure **composition** of ligand or antiligand.

L14 ANSWER 38 OF 45 USPATFULL

ACCESSION NUMBER: 80:56608 USPATFULL
TITLE: Antienzyme homogeneous competitive binding assay
INVENTOR(S): Yoshida, Robert A., Mountain View, CA, United States
Maggio, Edward T., Redwood City, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4233401		19801111	
APPLICATION INFO.:	US 1977-815487		19770714	(5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wiseman, Thomas G.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 1473
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Competitive protein binding methods and **composition** combinations for use in the methods are provided for determining an analyte which is a member of an immunological pair. . .

SUMM Analyte-the compound or **composition** to be measured, which may be mono- or polyepitopic, antigenic or haptenic, a single or plurality of compounds which share. . .

SUMM Receptor-any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. an epitopic site, and normally polyvalent i.e.. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . aminoalkyl benzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes

ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . residue was dissolved in 8.5 ml dry THF. To the solution was added 76 ml of ethyl acetate and the **mixture** vigorously shaken. The resulting suspension was gravity filtered and the filtrate washed in a separatory funnel with 10 ml water,. . .

DETD . . . a reaction flask was charged 7 mg of the T.sub.3 -MEMIDA prepared above, 344 .mu.l of dry THF, the reaction **mixture** cooled to ice bath temperature, followed by the addition of 46 .mu.l of the NHS solution and 55 .mu.l of the DCC solution. The reaction **mixture** was protected from light and was agitated in the cold room (2.degree.) for about 27 hrs. The solution was stripped. . .

DETD . . . solution introduced into a reaction flask equipped with stirrer and the solution cooled in an ice bath. While cooling the **mixture**, 1 ml of DMF was added at a rate of 150 .mu.l per minute, and then 1 ml was withdrawn.. . . between additions. After each addition, the enzyme activity in the presence and absence of anti (T-3) was assayed. The reaction **mixture** was placed in a 23 mm (25,000 mw cut-off) Spectrapor dialysis bag and dialyzed against 2.times.0.5 l. of 0.05 M. . .

DETD . . . at ice bath temperature, the reaction was allowed to continue for an additional 90 min. at room temperature. The reaction **mixture** was chromatographed on a Sephadex G-50 M column in the tris-buffer previously described and eluted with the same buffer at. . .

DETD . . . saturated sodium chloride and dried over anhydrous sodium sulfate. Evaporation of solvent gave a solid which was recrystallized from a **mixture** of methanol-ethyl acetate-hexane to yield a white solid (188 mg, mp. 202.degree.-220.degree. (dec)).

DETD . . . mmole) of dry triethylamine added through the serum stopper with a syringe with stirring at room temperature. After cooling the **mixture** to -14.degree., 9.34 .mu.l (0.05 mmole) of carbitol chloroformate was added below the surface of the solution and the **mixture** stirred for 30 minutes.

DETD . . . cup and employing a flow cell, reading the enzyme activity over a 60 second interval in a Gilford spectrophotometer.) The **mixture** is cooled to 0.degree. and with stirring 1.08 ml carbitol added slowly with a syringe below the surface of the. . .

DETD . . . was added with stirring at room temperature 100 .mu.l of a 1% solution in 95% ethanol of fluorodinitrobenzene and the **mixture** allowed to stir for one hour while shielded from direct light. Sodium periodate (1 ml, 40 mM), was added and the **mixture** stirred for 0.5 hr. under the same conditions, followed by the addition of 0.5 ml of 0.34 M aqueous ethylene glycol. After stirring for an additional hour under the same conditions, the reaction **mixture** was transferred to a dialysis bag and dialyzed against 3.times.900 ml of 10 mM NaHCO.sub.3 buffer (pH 9.5) in the. . .

DETD . . . .mu.mole) was added with stirring at 2.degree.-4.degree., 0.95 ml of the hIgG dialyzed residue (5 mg, 3.1.times.10.sup.-2 .mu.mole) and the **mixture** stirred for 45 min. To the **mixture** was

then added 5 mg (1.32.times.10.sup.-4 mole) of NaBH.sub.4, the **mixture** stirred for about 4.5 hrs. at 2.degree.-4.degree. and then dialyzed against 2.times.300 ml of PBS (10 mM Na.sub.2 HPO.sub.4, 0.15. . .

DETD . . . ml of deionized water adjusted to pH 10 with sodium hydroxide. After stirring for 5 min. at about 4.degree., the **mixture** was then stirred at room temperature for 25 min. A second addition of an equal amount of ethyl acetimidate was. . .

DETD A Sephadex G-200 column was prepared by first swelling the Sephadex G-200 in PBS, pH 6.7, by heating the **mixture** in a boiling water bath for 9 hrs. A 2.times.89 cm column was prepared and a portion of the above. . .

DETD . . . mole hIgG) was added 1 ml of 0.06 M sodium periodate (6.times.10.sup.-5 mole) in water at pH 8.1 and the **mixture** stirred for 3.5 hrs. at room temperature. To the **mixture** was then added 1 ml of 0.16 M aqueous ethylene glycol and the **mixture** stirred for 1.5 hrs. at room temperature. The reaction **mixture** was then transferred to a dialysis bag and dialyzed against 3.times.500 ml of 50 mM NaHCO.sub.3 buffer, pH 9, followed. . .

DETD . . . were combined to provide a final volume of 6.6 ml which was stirred while cooled in an ice bath. The **mixture** was then allowed to warm to room temperature and stirring continued for 4 hrs. After cooling the **mixture** in an ice water bath, 5 mg of NaBH.sub.4 were added and the **mixture** maintained in an ice bath for 3.5 hrs. The solution was then transferrred to the dialysis bag

and exhaustively dialyzed at 2.degree.-4.degree. against a buffer solution, 10 mM K.sub.2 HPO.sub.4 containing 0.15 M NaCl, pH 9. The reaction **mixture** was then concentrated in a collodion bag apparatus versus PBS, pH 7.0 to a volume of 2.4 ml.

DETD A 2.times.84 cm chromatographic column was prepared of Sephadex G-200 in

a PBS, pH 7.0. The reaction **mixture** was applied to the column and eluted with PBS, pH 7.0, at room temperature, coolecting 40 drop fractions. The column. . .

DETD . . . solution centrifuged at 10 K for 5 min at 4.degree. and the pellet isolated. The pellet was dissolved in a **mixture** of DMF/0.1 M bicarbonate buffer, pH9 and a 20 mg/ml solution of o-dianisidine in the same **mixture** added to provide a 1:10 mole ratio of the Dextran 10 to the o-dianisidine. The pH was adjusted to 9. . .

DETD To the **mixture** was then added 100 .mu.l of 1 M aqueous 1-amino-2-propanol, the pH adjusted to 9 with 1 N HCl and the **mixture** allowed to stand at room temperature in the dark for 3 hrs. The pH was then adjusted to 7, centrifuged. . .

DETD . . . (pH 7.8) to give a 0.1% egg albumin solution at pH 7.8). To the

solution was then added a preincubated **mixture** of 25 .mu.l antidigoxin (1 .mu.l of antidigoxin diluted with buffer) 1 ml of assay buffer and 2 .mu.l of. . . After incubating for 10 min. at 30.degree., 50 .mu.l of 80 mM .beta.-NAD (pH 5.1) at 30.degree. is added, the **mixture** assayed for 0.5 min. at 340 nm, 30.degree., followed by adding 5 .mu.l of anti G-6-PDH and assaying at 340. . .

DETD . . . with 200 .mu.l of buffer to which is added 20 .mu.l of hIgG and

2 .mu.l of anti hIgG. The **mixture** is incubated for 0.5 hrs. at 30.degree. followed by the addition of 4 .mu.l of anti-HRP and incubation for an additional 0.5 hrs. To the **mixture** is then added 1.8 ml of buffer having 0.22 mM o-dianisidine in the buffer and

ml of 22 mM. . .

DETD . . . 4, employing the enzyme G-6-PDH. Fraction 42 of that preparation is employed. The assay is carried out by preparing a **mixture** of 0.2 ml of fraction 42 in 0.2 ml of a 3.68.times.10.sup.-5 M solution of anti-hIgG in buffer, 10 mM. . . 7.48. The concentration of hIgG in fraction 42 is 2.54.times.10.sup.-2 mg/ml, while the concentration of G-6-PDH is 1.58.times.10.sup.-2 mg/ml.

The **mixture** is incubated at 30.degree. for over 30 min. A solution is prepared of 1.6 ml buffer, 0.05 ml G-6-P and. . .

DETD . . . 20, 9.6 mg/ml) and hIgG (final concentration 10.sup.-6) added, followed by a 20 min incubation at room temperature. To the **mixture** is then added 5 .mu.l 22 mM H.sub.2 O.sub.2 and the change in absorbance at 460 nm at 30.degree. over. . .

CLM What is claimed is:

20. An assay **composition** for use in the method according to claim 1 comprising enzyme-bound-ligand; ligand receptor and enzyme inhibitor of at least 2,000. . .

21. An assay **composition** according to claim 20, wherein said enzyme inhibitor is antienzyme.

22. An assay **composition** according to claim 20, wherein said enzyme inhibitor is a macromolecular inhibiting enzyme substrate.

23. An assay **composition** for use in the method according to claim 1 for determining antiligand comprising enzyme-bound-ligand and enzyme inhibitor of at least. . .

L14 ANSWER 39 OF 45 USPATFULL

ACCESSION NUMBER:	80:43095 USPATFULL
TITLE:	Method for conjugating to polyamino compounds employing haloacyl groups and compositions prepared thereby
INVENTOR(S):	Rowley, Gerald L., San Jose, CA, United States Leung, Danton, Campbell, CA, United States Singh, Prithiphal, Santa Clara, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4220722		19800902	
APPLICATION INFO.:	US 1978-876772		19780210	(5)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Shapiro, Lionel M.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1
LINE COUNT:	1446

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of interest, but the analyte having the protective groups. This may result in substantially reducing the specificity of the antibody **composition** for the analyte of interest.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives are metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, methyldopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM . . . miscellaneous individual drugs which include methadone, phenoxybenzamine and related haloalkylamines, tolamol, sotalol, guanethide, meprobamate, serotonin, merperidine, chlorcyclazine, chlorpheniramine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, methotrexate, aminopterin, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Depending upon the particular compounds involved, other ancillary materials may also be included in the reaction **mixture**.

DETD . . . hydrochloride (ECDI) were added with stirring. After stirring for a short while the temperature was raised to 0.degree. and the **mixture** stirred for an additional 5 hrs., followed by storage at 4.degree. for about 30 hrs.

DETD The second fraction was evaporated to dryness to yield an oily solid weighing 57 mg. The product was a **mixture** of starting materials and product. Some removal of the bromoacetic acid was achieved by dissolving the **mixture** in chloroform, extracting with 3-4 ml portions of water and then extracting the aqueous portions with 3-4 ml portions of. . .

DETD The entire product was dissolved in 200 .mu.l of anhydrous DMF and 150 .mu.l of anhydrous diglyme and the **mixture** stirred overnight under argon. To an aliquot of 89 .mu.l was added 50 .mu.l of anhydrous DMF containing 10 .mu.M. . .

DETD . . . phosphate followed by the further addition of 93 .mu.l of water to provide a total volume of 1.03 ml. The **mixture** was cooled to 0.degree. and the addition of the above NHS ester solution added slowly with vigorous stirring in aliquot. . .

DETD . . . aminoethanethiol (39 mg, 0.5 mmol) and triethylamine (210 ml, 1.5 mmol) in 1.0 ml of anhydrous dimethylformamide under nitrogen. The **mixture** was allowed to warm to room temperature over 11/2 hours, the solvent was removed in vacuo at 40.degree., and the. . . taken up in 3 ml of water and treated with 20 ml of 0.10 M sodium carbonate. Extraction of the **mixture** with ethyl acetate, washing with water, and evaporation in vacuo yielded a glass. To this glass were added under nitrogen,. . .

DETD . . . homogeneous enzyme immunoassay. By adding the antibody to a sample containing morphine or a morphine derivative i.e. codeine, when the **mixture** is added to the enzyme conjugate, there is no inhibition. Thus, the product can be used in a homogeneous enzyme. . .

DETD . . . added 200 .mu.l of a chilled DMF solution containing 44 .mu.M of NHS and 40 .mu.M of ECDI and the **mixture** allowed to stand 2 days at 4.degree. under argon.

DETD To the stirred **mixture** was added slowly in primarily 5 .mu.l increments the NHS ester prepared above with invervening additions of 1 N sodium. . .

DETD . . . solution saturated with argon for 40 min (5.5 ruby ball) and
50
.mu.l of the morphinethiol solution added slowly. The **mixture**
was then stored under argon at 4.degree. for 30 days. At the end of
this
time, the **mixture** was transferred to a dialysis sack and
dialyzed against 5.times.125 ml portions of 0.01 M phosphate, pH 7.0
for
several. . .
DETD . . . was suspended in 100 ml of anhydrous methanol. Ammonia gas was
introduced with stirring. The suspension became thinner and the
mixture began to warm up. The **mixture** was cooled by
ice bath and saturated with NH.sub.3 for one hour. After filtration the
solid cake was treated once. . .
DETD . . . was packed with 500 g (60-200 mesh) of silica gel. The eluent
is the lower phase of the following solvent **mixture**:
CHCl.sub.3 /isopropyl alcohol/17% NH.sub.4 OH in a ratio of 2/1/1.
DETD Five grams of gentamicin complex was dissolved in a **mixture** of
methanol and chloroform. To this solution was added silica gel (5 g)
and
the **mixture** concentrated to a dry powder. The **mixture**
was placed on the top of the column, wetted with solvent, topped with
2-3 cm of sand and covered with. . . Gentamicin C.sub.1 collected
pure at 5 l. to 5.65 l. weighed 610 mg. It followed a long fraction of
a
mixture of C.sub.1 and C.sub.2. Then 900 mg of gentamicin
C.sub.2 was collected. The pure C.sub.1a isomer isolated was very
small.
. .
DETD . . . methanol under argon and at room temperature. To this solution
was added ethyl trifluoroacetate (1 mmol, 160 mg) and the
mixture was stirred overnight. Analytical tlc (silica,
CHCl.sub.3 /MeOH/conc. NH.sub.4 OH:10/10/3) showed approximately 60%
reaction but further reaction did not improve. . .
DETD . . . mmol) was placed in a dropping funnel with a dry ice jacket
and
was added over an hour. The resulting **mixture** was stirred at
room temperature for an additional hour. Concentration on a warm water
bath and oil pump gave 1.6. . .
DETD . . . in five minutes. The reaction was vigorous with gasing after
the addition of 1.5 ml of Et.sub.3 N. The reaction **mixture** was
stirred at room temperature for two hours and then subjected to
degasing
under the water aspirator. To the resulting **mixture** was added
20 ml of water and the aqueous solution extracted with 50 ml of
CH.sub.2
Cl.sub.2. The aqueous layer. . . with 50 ml of saturated
NaHCO.sub.3.
Upon acidification with 5 N H.sub.2 SO.sub.4 to pH 2 and extraction by
a
mixture of CH.sub.2 Cl.sub.2 -CHCl.sub.3 (total 120 ml), the
product solution was washed with saturated brine and dried
(MgSO.sub.4).
Concentration of. . .
DETD . . . 2'-N-trifluoroacetylgentamicin C.sub.1 (0.19 mmol, 107 mg) in
8
ml of dry THF. The addition took 0.5 hour and the reaction
mixture was allowed to proceed at room temperature overnight.
The resulting **mixture** was concentrated and passed through a
small silica gel column, first with 1:1 chloroform-hexane, then 10%
MeOH

in chloroform and. . .

DETD . . . (0.2 mM, 38 mg) were dissolved in 1 ml of anhydrous DMF in an ice bath under argon. The capped **mixture** was stirred in a cold room overnight. The tan colored solution was stored in the freezer ready for use.

DETD . . . under nitrogen was added slowly a solution of 0.08 g (0.5 mmol) of homocysteinthiolactone in 2 ml of THF. The **mixture** was then stirred at room temperature under nitrogen for 2 hrs and could then be used directly for conjugation to. . .

DETD . . . ml of triethylamine in 10 ml of methylene dichloride at 0.degree. was added 1.86 g (10 mmol) of 2,4-dinitrofluorobenzene. The **mixture** was then stirred at room temperature overnight and the volatiles removed in vacuo to leave a yellow residue. The residue. . .

DETD . . . (1 mmol) of N-hydroxy succinimide. Under nitrogen at 0.degree. was then added 0.287 g (1.5 mmol) of ECDI and the **mixture** stirred at 0.degree. for 2 hrs followed by adding the **mixture** dropwise to a solution of 0.467 g (1 mmol) of tobramycin in a **mixture** of 12 ml water and 3 ml DMF. After stirring overnight at 0.degree., the solvent was removed in vacuo to. . .

DETD . . . a solution of 2.01 ml (0.024 mol) of bromoacetyl bromide in 10 ml of methylene dichloride. After the addition, the **mixture** was stirred for 3 hrs and poured into 1 N aqueous hydrochloride. The organic layer was separated and then washed successively with 1 N HCl, water and brine. After drying over anhydrous sodium sulfate, the **mixture** was evaporated to dryness in vacuo to yield 6 g of a light brown product, which upon recrystallization from hexane-ethyl. . .

DETD . . . C. in an inert polar solvent. Illustrative solvents include tetrahydrofuran, dimethylformamide, ethyleneoxy and propyleneoxy ethers, and the like. The reaction **mixture** may then be worked up in conventional ways, the disulfide cleaved to provide a thio compound, which may then be. . .

L14 ANSWER 40 OF 45 USPATFULL

ACCESSION NUMBER:	80:42825 USPATFULL
TITLE:	Chemically induced fluorescence immunoassay
INVENTOR(S):	Maggio, Edward T., Redwood City, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4220450		19800902	
APPLICATION INFO.:	US 1978-893910		19780405	(5)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Marantz, Sidney			
LEGAL REPRESENTATIVE:	Rowland, Bertram I.			
NUMBER OF CLAIMS:	32			
EXEMPLARY CLAIM:	1			
LINE COUNT:	1336			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of another molecule. For the most part, these compounds are antibodies, which are able to distinguish between the compound or **composition** of interest, and other compounds of analogous structure. By virtue of the binding of the receptor to a labeled

ligand,. . .

SUMM Analyte--the compound or **composition** to be measured, which may be a ligand which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor--any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM Poly(ligand analog)-label--a **composition** in which a plurality of ligand analogs and one or a plurality of labels are bonded together whereby the ligand. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, detromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . is aminoalkylbenzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

DETD . . . 8.1, was introduced 6 mg horseradish peroxidase (HRP) and 100 .mu.l of a 1% aqueous solution of 2,4-dinitro-1-fluorobenzene and the **mixture** incubated for 1 hr. The **mixture** was then dialzyed against 0.01 M sodium carbonate, pH 9.5 for 2 hrs followed by dialysis against 0.3 M sodium. . .

DETD . . . 1.5 ml solution of the HRP material prepared above was added to 1 ml 0.4 M sodium periodate and the **mixture** allowed to stand for 45 min at room temperature. To the solution was then added 25 .mu.l of 0.32 M aqueous ethylene glycol, the **mixture** allowed to stand for 1 hr, followed by dialysis for 2 hrs in a collodion bag apparatus against 0.01 M sodium carbonate, pH 9.5. The residue in the dialysis bag was then combined with 5 mg hIgG and the **mixture** allowed to stand for 1 hr. At this time, 15 mg sodium borohydride was added, the **mixture** allowed to stand for 1.25 hrs at room temperature and the product then dialyzed overnight in a collodion bag apparatus. . .

DETD . . . vial fitted with stirring bar was introduced 5 mg lyophilized rabbit anti(hIgG) (Miles Laboratories, Lot 18, Code 64-155) and the **mixture** dissolved in 0.5 ml aqueous sodium phosphate, pH 8.0 and the pH adjusted to 9 with aqueous sodium carbonate buffer.. . . of 0.3 mg fluorescein isothiocyanate in 0.3 ml DMF was added over about 40 secs with vigorous stirring and the **mixture** stirred for 60 min. At the end of this time, the reaction **mixture** was chromotographed on a Sephadex (G-25) column and the fractions collected.

A fraction was obtained having 2.4 mg/ml of a. . .

L14 ANSWER 41 OF 45 USPATFULL
ACCESSION NUMBER: 80:29494 USPATFULL
TITLE: Label modified immunoassays
INVENTOR(S): Zuk, Robert F., Mountain View, CA, United States
Maggio, Edward T., Redwood City, CA, United States
PATENT ASSIGNEE(S): Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4208479		19800617	
APPLICATION INFO.:	US 1977-815632		19770714	(5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wiseman, Thomas G.
LEGAL REPRESENTATIVE: Rowland, Bertram I.
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1,8,13,19,22
LINE COUNT: 1595
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . substantial loss of the desired antibodies as well as reduction in the binding constant. That is, those antibodies in the **composition** which have the strongest binding, frequently cannot be removed from the column. Therefore, most methods have avoided labeling antibodies, since. . .
SUMM Analyte--the compound or **composition** to be measured, which may be a ligand which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .
SUMM Label--a compound or **composition** capable of providing a detectable signal in conjunction with physical activation (or excitation) or chemical reagents and capable of being. . .
SUMM Receptor--Any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. an epitopic site. Illustrative receptors include naturally. . .
SUMM Receptor (antiligand) may be a **mixture** of labeled and unlabeled receptor, generally having from about 5 to 100% of the receptor as labeled receptor. The proportion. . .
SUMM . . . hours, usually not exceeding twelve hours, and more usually not exceeding six hours. After adding each component to the assay **mixture**, different incubation periods before adding the next component or taking the measurement will be involved. Since the ultimate results will. . .
SUMM The microorgaisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:
SUMM Clostridium **botulinum**
SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .
SUMM . . . aminoalkyl benzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their

metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and derivatives.

SUMM Metabolites related to diseased states include spermine, galactose, phenylpyruvic acid, porphyrin type 1, vanillomandelic acid, **epinephrine** and norepinephrine

SUMM For monoepitopic analytes, it is necessary to prepare a polyepitopic **composition** having a plurality of epitopic sites capable of competing with the ligand. This normally involves modification of the ligand to. . .

SUMM . . . when the receptor is bound to analyte. Third, the label must be capable of modification by a macromolecular compound or **composition**, so as to modify the signal preferably by diminishing the signal to be measured. In addition, desirable labels are stable,. . .

DETD . . . the addition of an aqueous solution of 2 M hydroxylamine and 2 M NaCl, the ice bath removed and the **mixture** stirred at room temperature for 1 hr. After dialyzing against 1.times.350 ml of 0.1 M sodium phosphate and 0.1 M. . .

DETD . . . a total volume of 1 ml and 100 .mu.l of 1% 2,4-dinitrofluorobenzene in 95% ethanol added with stirring and the **mixture** stirred for 1 hr. at room temperature while protected from light. To the **mixture** was then added dropwise 1 ml of an aqueous 30.2 mM sodium periodate solution, the **mixture** stirred for 0.5 hr. protected from light, followed by the addition of 1 ml of an aqueous 0.34 M ethylene glycol solution, the **mixture** stirred for 0.75 hr. and then dialyzed with 2.times.350 ml of ice cold 10 mM sodium bicarbonate-sodium carbonate buffer (pH. . .

DETD . . . product solution. The HRP/anti(hIgG)M ratio was 4.2. After stirring for 0.5 hr, 5.05 mg of sodium borohydride was added, the **mixture** stirred at ice bath temperature for 5.5 hours, followed by dialysis 1.times.350 ml of 0.1 M sodium phosphate and 0.1. . .

DETD . . . lot #R220) (carbonate, 0.1 M, pH 9.0) was added 50 .mu.l of fluorescein isothiocyanate (4 mg/ml) in DMF and the **mixture** stirred at room temperature for two hours. The reaction solution was then transferred to a 0.9.times.25 cm Sephadex G-25 column. . .

DETD . . . containing 0.06% egg alumin and 0.05 NaN.sub.3 was added 100 .mu.l of hIgG in the above PBS buffer and the **mixture** incubated for 45 min. at room temperature. To the solution was then added 2.8 ml of buffer and 7 .mu.l. . .

CLM What is claimed is:

29. An assay **composition** for use in an assay method according to claim 1 which comprises the reagents labeled anti(ligand) and macromolecular modifier in. . .

30. An assay **composition** according to claim 29 wherein said modifier is anti(label).

31. An assay **composition** according to claim 29, including poly(ligand analog).

32. An assay **composition** according to claim 29, including polyepitopic ligand.

instances, the fluorescer and quencher will be interchangeable, although
there will frequently. . .

SUMM Receptor **composition**--receptor **composition** is a homogeneous or heterogeneous **composition** capable of specific non-covalent binding to ligand and ligand analog and includes anti-ligand (a **composition** which specifically recognizes the ligand) and a combination of anti-ligand and anti(anti-ligand) (a **composition** which specifically recognizes the anti-ligand).

SUMM . . . on the employment of two chromophores which form a fluorescer-quencher pair. One of the chromophores is covalently bonded to a **composition** (receptor) which specifically recognizes or binds to a ligand. The other chromophore is covalently bonded to ligand analog or receptor.. . .

SUMM . . . the assay medium: ligand analog-chromophore, poly(ligand analog)-poly(chromophore), poly(ligand analog), one or two receptors and
one or two receptor-chromophores. The first **composition** to be considered will be the ligand analog-chromophore.

SUMM . . . should also be noted that when antibodies are prepared for a ligand having a plurality of epitopic sites, the receptor **composition** is not homogeneous. That is, the receptor will have antibodies which recognize different epitopic sites. In referring to receptor, it. . .

SUMM . . . the nucleus molecule be water soluble, in most instances, it will be desirable. In any event, the nucleus molecule or **composition** will be capable of stable dispersion in an aqueous medium. Secondly, the nucleus molecule should not absorb light at the. . .

SUMM The next group of alkaloids are the **cocaine** alkaloids, which includes, particularly as metabolites, benzoyl ecgonine and ecgonine.

SUMM The alkaloids of primary interest are those which come within the category of drugs of abuse, such as morphine, **cocaine**, mescaline, and lysergic acid, which may be analyzed for the compound or its metabolite, depending on the physiological fluid which. . .

SUMM Drugs of interest because of their physiological properties are those which are referred to as catecholamines. Among the catecholamines are **epinephrine**, ephedrine, L-dopa, and norepinephrine.

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . In this manner, the ratio of the two common receptors can be carefully controlled and accurately added to the assay **mixture**. The **mixture** can be a dry lyophilized **mixture** or an aqueous, normally buffered (pH 5-10; usually 6.5-8.5) solution of any desired concentration.

SUMM . . . a matter of operability, but rather expedience. In most cases, the receptor is antibody, which will be a complex protein **mixture**, containing antibody for the ligand, as well as other antibodies and proteins. When the antibody **composition** is labeled with chromophore, a substantial proportion of the chromophore will be bound to protein other than the antibody for. . .

SUMM . . . the two conjugated antibodies are combined with the unknown to be assayed, incubated, and the poly(ligand analog) added and the **mixture** further incubated. The times and temperatures previously indicated are also applicable in this assay.

SUMM . . . chromophore, particularly quencher, is conjugated to anti(anti-ligand) to provide anti(anti-ligand)-chromophore, which is

employed in conjunction with anti-ligand as a receptor **composition** for ligand. In this manner, one can bind a larger number of quencher molecules to the ligand, enhancing the opportunity. . .

DETD B. O.sup.3 -aminoethylmorphine (100 mg) is dissolved in 5 ml of acetone and added to a **mixture** of acetone (20 ml), water (5 ml), and triethylamine (0.07 ml). To this solution is added a solution of FITC. . . with stirring during 15 min. Stirring is continued for an additional 80 min, while adjusting the pH of the reaction **mixture** to 9.5 with drops of dilute triethylamine solution in acetone (1.4 ml/10 ml acetone). The acetone is then partially removed. . .

DETD . . . O.sup.3 -carboxymethylmorphine and isobutyl chloroformate (0.1 mmole, large excess) in DMF (2 ml) added in the cold (0.degree.), and the **mixture** allowed to react for 3 hours. The gel was filtered and washed successively with H.sub.2 O (500 ml), 0.1 M. . .

DETD . . . and then stays stable, and is maintained at 9.0-9.5 if necessary, by careful addition of crystalline potassium carbonate. The reaction **mixture** is then applied to a Sephadex G-25(M) column (1.times.15 cm) with 0.01 M phosphate buffer pH 7.5 and elution of. . .

DETD . . . pH 9.5 with crystalline Na.sub.2 CO.sub.3. TRITC (0.5 mg) in acetone (20-30 .mu.l) was added at room temperature and the **mixture** stirred for 3 hrs. A precipitate formed which was removed by centrifugation and discarded. The conjugate was then separated twice. . .

DETD . . . M hydroxylamine hydrochloride, which had been neutralized with 10 N NaOH, was added. Stirring was continued for 1 hr., the **mixture** then centrifuged on a Brinkmann centrifuge for 3 min., and a little precipitate was removed. The supernatant was separated on Sephadex LH-20 column (0.9.times.15 cm) equilibrated with a **mixture** of 20 parts glycerol and 80 parts of 0.1 M phosphate buffer pH 8.0. The eluted conjugate solution was diluted 1:1.5 with the same glycerol-phosphate **mixture**.

DETD . . . of morphine (5-10 .mu.l of the standard morphine solutions) for one hour. FLUMO'S' (10 .mu.l) was then added and the **mixture** incubated for an additional one hour. The final volume of each tube was 3 ml. The final concentration of FLUMO'S'. . .

DETD . . . 1.5.times.10.sup.-6 M bovine gamma-globulin (390-430 .mu.l) Codeine in increasing concentrations (1.5.times.10.sup.-3 -1.5.times.10.sup.-6 M) is then added (10-40 .mu.l) and the **mixture** incubated at room temperature for 0.5 hr. To each of the tubes is then added 10 .mu.l (0.24 .mu.g) of. . .

DETD In 2.4 ml buffer is introduced 0.025 ml each of the appropriate calibrator, fluorescein conjugate and rhodamine conjugate, the **mixture** incubated for 50 min. at room temperature and the fluorescence read. The following table indicates the results.

DETD

Incubation

Mixture	Calibrator dilution	Reagent a	Reagent b	Buffer	% F*
1	1:18	+	+	+	44.6
2	1:11	+	+	+	49.6
3	1:8	+	+	+. . . . +	+ 95.7
8	--	+	-	+	100

*% F indicates % of maximum fluorescence, the value obtained with

Incubation **Mixture** 8.

DETD . . . bonded to a chromophore and antibody employed which is conjugated to the other member of the fluorescer-quencher pair or the **mixture** of antibodies indicated above employed. The assay is relatively rapid, and depending upon the concentrations, various incubation times are required.. . .

CLM What is claimed is:

. . . form an assay solution; (1) said unknown; (2) a source of Ch.sub.1 as Ch.sub.1 covalently bound to a first antibody **composition** capable of specific non-covalent binding to said ligand of said sample antibody; (3) a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second antibody **composition** capable of specific non-covalent binding to said ligand or as Ch.sub.2 covalently or non-covalently bound to ligand analog, wherein ligand. . . to the binding sites of said antibodies, with the proviso that when Ch.sub.2 is present bound to said second antibody **composition**, ligand is added to said medium; (B) incubating said assay solution for a sufficient time for at least a portion. . .

. . . form an assay solution; (1) said unknown; (2) a source of Ch.sub.1, as Ch.sub.1 covalently bound to a first receptor **composition** capable of specific non-covalent binding to said ligand; (3) a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second receptor **composition** capable of specific non-covalent binding to said ligand or as Ch.sub.2 covalently or non-covalently bound to ligand analog, wherein ligand. . . be assayed is present in said unknown and said source of Ch.sub.2 is Ch.sub.2 covalently bound to said second receptor **composition**, ligand is added to said medium; (B) incubating said assay solution for a sufficient time for at least a portion. . .

11. A method according to claim 10, wherein ligand is present in said unknown, said first receptor **composition** is a combination of anti-ligand from a first species and anti(first anti-ligand) conjugated to Ch.sub.1, and said second receptor **composition** is anti-ligand from a second species and anti(second anti-ligand) conjugated to Ch.sub.2.

23. A method for determining in an assay solution the presence of an antibody in a sample suspected of containing. . . form an assay solution; (1) said unknown; (2) a source of Ch.sub.1 as Ch.sub.1 covalently bound to a first antibody **composition** capable of specific non-covalent binding to said ligand; (3) a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second antibody **composition** capable of specific non-covalent binding to said ligand; (4) ligand; (B) incubating said assay solution for a sufficient time for. . .

. . . form an assay solution; (1) said unknown; (2) a source of Ch.sub.1 as Ch.sub.1 covalently bound to a first antibody **composition** capable of specific non-covalent binding to said sample antibody; (3) a source of Ch.sub.2, as Ch.sub.2 covalently bound to a second antibody **composition** capable of specific non-covalent binding to said ligand or as Ch.sub.2 covalently or non-covalently bound to ligand analog, wherein ligand. . . to the binding sites of said antibodies, with the proviso that when Ch.sub.2 is present bound to said second antibody **composition**, ligand is added to said medium; (B)

incubating said assay solution for a sufficient time for at least a portion. . .

L14 ANSWER 43 OF 45 USPATFULL

ACCESSION NUMBER:	79:45608 USPATFULL
TITLE:	Fluorescence quenching with immunological pairs in immunoassays
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Schwarzberg, Moshe, Palo Alto, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4174384		19791113	
APPLICATION INFO.:	US 1976-731255		19761012	(5)
DISCLAIMER DATE:	19931207			

RELATED APPLN. INFO.: Continuation of Ser. No. US 1975-591386, filed on 30 Jun 1975, now patented, Pat. No. US 3996345 which is a continuation-in-part of Ser. No. US 1974-497167, filed on 12 Aug 1974, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Fagelson, Anna P.
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	4
EXEMPLARY CLAIM:	1
LINE COUNT:	1556

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . to a hub molecule, usually a polymer, in combination with antibody bound to the other of the F-Q pair. The **composition** is irradiated with light at a wavelength, absorbed by the fluorescing molecule and the amount of fluorescence determined. By employing. . .

SUMM One chromophore is introduced into the assay medium covalently bonded to a receptor **composition** which specifically binds to the ligand. The second chromophore can be introduced into the assay medium in different ways: (1) covalently bonded to a receptor **composition** which is the same or different from the receptor **composition** conjugated to the first chromophore, but in both instances specifically binds to the ligand, and in the presence or absence of polyligand; or covalently bonded to ligand analog, where the ligand analog can compete with ligand for the receptor **composition**. The choice of modes of introduction will depend to a significant degree on the number of independent epitopic or haptenic. . .

DETD . . . fluorescer molecule, by accepting the energy which would otherwise be emitted as fluorescent light. As far as the molecule or **composition** to which the chromophores are joined, in most instances, the fluorescer and quencher will be interchangeable, although there will frequently. . .

DETD Receptor **composition**--receptor **composition** is a homogeneous or heterogeneous **composition** capable of specific non-covalent binding to ligand and ligand analog and includes anti-ligand (a **composition** which specifically recognizes the ligand) and a combination of anti-ligand and anti(anti-ligand) (a **composition** which specifically recognizes the anti-ligand).

DETD . . . on the employment of two chromophores which form a fluorescer-quencher pair. One of the chromophores is covalently bonded to a **composition** (receptor) which specifically recognizes or

binds to a ligand. The other chromophore is covalently bonded to ligand analog or receptor.. . .

DETD . . . the assay medium: ligand analog-chromophore, poly(ligand analog)-poly(chromophore), poly(ligand analog), one or two receptors and one or two receptor-chromophores. The first **composition** to be considered will be the ligand analog-chromophore.

DETD . . . should also be noted that when antibodies are prepared for a ligand having a plurality of epitopic sites, the receptor **composition** is not homogeneous. That is, the receptor will have antibodies which recognize different epitopic sites. In referring to receptor, it. . .

DETD . . . the nucleus molecule be water soluble, in most instances, it will be desirable. In any event, the nucleus molecule or **composition** will be capable of stable dispersion in an aqueous medium. Secondly, the nucleus molecule should not absorb light at the. . .

DETD The next group of alkaloids are the **cocaine** alkaloids, which includes, particularly as metabolites, benzoyl ecgonine and ecgonine.

DETD The alkaloids of primary interest are those which come within the category of drugs of abuse, such as morphine, **cocaine**, mescaline, and lysergic acid, which may be analyzed for the compound or its metabolite, depending on the physiological fluid which. . .

DETD Drugs of interest because of their physiological properties are those which are referred to as catecholamines. Among the catecholamines are **epinephrine**, ephedrine, L-dopa, and norepinephrine.

DETD The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

DETD . . . tularensis

Brucellae
Brucella melitensis
Brucella abortus
Brucella suis
Aerobic Spore-forming Bacilli
Bacillus anthracis
Bacillus subtilis
Bacillus megaterium
Bacillus cereus
Anaerobic Spore-forming Bacilli
Clostridium **botulinum**
Clostridium tetani
Clostridium perfringens
Clostridium novyi
Clostridium septicum
Clostridium histolyticum
Clostridium tertium
Clostridium bifermentans
Clostridium sporogenes
Mycobacteria
Mycobacterium tuberculosis hominis
Mycobacterium. . .

DETD . . . In this manner, the ratio of the two common receptors can be carefully controlled and accurately added to the assay **mixture**. The **mixture** can be a dry lyophilized **mixture** or an aqueous, normally buffered (pH 5-10; usually 6.5-8.5) solution of any desired concentration.

DETD . . . a matter of operability, but rather expedience. In most cases, the receptor is antibody, which will be a complex protein

33. An assay **composition** for use in a method according to claim 9 which comprises the reagents enzyme labeled anti(ligand) and anti(enzyme) in relative. . .

34. An assay **composition** for use in a method according to claim 33, which comprises the reagents fluorescer labeled anti(ligand) and anti(fluorescer) in relative. . .

35. An assay **composition** for use in a method according to claim 28 which comprises the combined reagents labeled anti(ligand) and Fab anti(label) in. . .

36. An assay **composition** according to claim 35, wherein said label is an enzyme.

37. An assay **composition** according to claim 35, wherein said label is a fluorescer.

L14 ANSWER 42 OF 45 USPATFULL

ACCESSION NUMBER:	80:19816 USPATFULL
TITLE:	Fluorescence quenching with immunological pairs in immunoassays
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Schwarzberg, Moshe, Sunnyvale, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4199559		19800422	
APPLICATION INFO.:	US 1977-766279		19770207	(5)
DISCLAIMER DATE:	19931207			

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1976-731255, filed on 12 Oct 1976, now Defensive Publication No. which is a continuation-in-part of Ser. No. US 1975-591386, filed on 30 Jun 1975, now patented, Pat. No. US 3996345 which is a continuation-in-part of Ser. No. US 1974-497167, filed on 12 Aug 1974, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Marantz, Sidney
LEGAL REPRESENTATIVE:	Rowland, Bertram I.
NUMBER OF CLAIMS:	26
EXEMPLARY CLAIM:	1
LINE COUNT:	2065

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM One chromophore is introduced into the assay medium covalently bonded to a receptor **composition** which specifically binds to the ligand. The second chromophore can be introduced into the assay medium in different ways: (1) covalently bonded to a receptor **composition** which is the same or different from the receptor **composition** conjugated to the first chromophore, but in both instances specifically binds to the ligand, and in the presence or absence of polyligand; or covalently bonded to ligand analog, where the ligand analog can compete with ligand for the receptor **composition**. The choice of modes of introduction will depend to a significant degree on the number of independent epitopic or haptenic. . .

SUMM . . . fluorescer molecule, by accepting the energy which would otherwise be emitted as fluorescent light. As far as the molecule or **composition** to which the chromophores are joined, in most

mixture, containing antibody for the ligand, as well as other antibodies and proteins. When the antibody **composition** is labeled with chorophore, a substantial proportion of the chromophore will be bound to protein other than the antibody for. . .

DETD . . . the two conjugated antibodies are combined with the unknown to be assayed, incubated, and the poly(ligand analog) added and the **mixture** further incubated. The times and temperatures previously indicated are also applicable in this assay.

DETD . . . chromophore, particularly quencher, is conjugated to anti(anti-ligand) to provide anti(anti-ligand)-chromophore, which is employed in conjunction with anti-ligand as a receptor **composition** for ligand. In this manner, one can bind a larger number of quencher molecules to the ligand, enhancing the opportunity. . .

DETD B. O.sup.3 -aminoethylmorphine (100 mg) is dissolved in 5 ml of acetone and added to a **mixture** of acetone (20 ml), water (5 ml), and triethylamine (0.07 ml). To this solution is added a solution of FITC. . . with stirring during 15 min. Stirring is continued for an additional 80 min, while adjusting the pH of the reaction **mixture** to 9.5 with drops of dilute triethylamine solution in acetone (1.4 ml/10 ml acetone). The acetone is then partially removed. . .

DETD . . . O.sup.3 -carboxymethylmorphine and isobutyl chloroformate (0.1 mmole, large excess) in DMF (2 ml) added in the cold (0.degree.), and the **mixture** allowed to react for 3 hours. The gel was filtered and washed successively with H.sub.2 O (500 ml), 0.1 M. . .

DETD . . . and then stays stable, and is maintained at 9.0-9.5 if necessary, by careful addition of crystalline potassium carbonate. The reaction **mixture** is then applied to a Sephadex G-25(M) column (1.times.15 cm) with 0.01 M phosphate buffer pH 7.5 and elution of. . .

DETD . . . pH 9.5 with crystalline Na.sub.2 CO.sub.3. TRITC (0.5 mg) in acetone (20-30 .mu.l) was added at room temperature and the **mixture** stirred for 3 hrs. A precipitate formed which was removed by centrifugation and discarded. The conjugate was then separated twice. . .

DETD . . . of morphine (5-10 .mu.l of the standard morphine solutions) for

one hour. FLUMO'S' (10 .mu.l) was then added and the **mixture** incubated for an additional one hour. The final volume of each tube was 3 ml. The final concentration of FLUMO'S'. . .

DETD . . . 1.5.times.10.sup.-6 M bovine gamma-globulin (390-430 .mu.l) Codeine in increasing concentrations (1.5.times.10.sup.-3 -1.5.times.10.sup.-6 M) is then added (10-40 .mu.l) and the **mixture** incubated at room temperature for 0.5 hr. To each of the tubes is then added 10 .mu.l (0.24 .mu.g) of. . .

DETD . . . bonded to a chromophore and antibody employed which is conjugated to the other member of the fluorescer-quencher pair or the **mixture** of antibodies indicated above employed. The assay is relatively rapid, and depending upon the concentrations, various incubation times are required.. . .

CLM What is claimed is:

1. A **composition** for determining the presence or amount of a ligand comprising two chromophores, which are a fluorescer-quencher pair, the amount of. . .

2. The **composition** of claim 1, which in addition includes one of said chromophores covalently bonded to an antibody to said anti-ligand.

3. The **composition** of claim 1, wherein said ligand is a

globulin.

4. The **composition** of claim 1, wherein said ligand is a hapten.

L14 ANSWER 44 OF 45 USPATFULL

ACCESSION NUMBER:	79:30628 USPATFULL		
TITLE:	Catalyst mediated competitive protein binding assay		
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States		
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4160645		19790710
APPLICATION INFO.:	US 1977-815636		19770714 (5)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Marantz, Sidney		
LEGAL REPRESENTATIVE:	Townsend and Townsend		
NUMBER OF CLAIMS:	27		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1398		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Analyte -- the compound or **composition** to be measured, which may be a ligand which is mono- or polyepitopic, antigenic or haptenic, a single or plurality. . .

SUMM Receptor -- any compound or **composition** capable of recognizing a particular spatial and polar organization of a molecule i.e. epitopic site. Illustrative receptors include naturally occurring. . .

SUMM Poly(ligand analog)-polylabel -- a **composition** whereby a plurality of ligand analogs and a plurality of labels are bonded to a water soluble polyfunctionalized hub nucleus,. . .

SUMM . . . in an assay for ligand, the unknown sample suspected of containing the ligand or antiligand may be first combined, the **mixture** incubated, followed by addition of the labeled ligand and a second incubation or alternatively, the unknown sample, labeled ligand and. . .

SUMM The microorganisms which are assayed may be intact, lysed, ground or otherwise fragmented, and the resulting **composition** or portion, e.g. by extraction, assayed. Microorganisms of interest include:

SUMM Clostridium **botulinum**

SUMM . . . interest are the alkaloids. Among the alkaloids are morphine alkaloids, which includes morphine, codeine, heroin, dextromethorphan, their derivatives and metabolites; **cocaine** alkaloids, which includes **cocaine** and benzoyl ecgonine, their derivatives and metabolites; ergot alkaloids, which includes the diethylamide of lysergic acid; steroid alkaloids; iminazoyl alkaloids;. . .

SUMM . . . aminoalkyl benzenes, with alkyl of from 2 to 3 carbon atoms, which includes the amphetamines, catecholamines, which includes ephedrine, L-dopa, **epinephrine**, narceine, papaverine, their metabolites and derivatives.

SUMM The next group of drugs is miscellaneous individual drugs which include methadone, meprobamate, serotonin, meperidine, amitriptyline, nortriptyline, **lidocaine**, procaineamide, acetylprocaineamide, propanolol, griseofulvin, butyrophenones, antihistamines, anticholinergic drugs, such as atropine, their metabolites and

derivatives.

SUMM For monoepitopic ligand analytes, the label may be conjugated to the ligand or a polyepitopic **composition** may be prepared having a plurality of epitopic sites capable of competing with the ligand and capable of being labeled. . .

SUMM The preparation of the polyepitopic **composition** normally involves modification of the ligand to provide for a linking group between a ligand and a hub nucleus, which. . .

DETD . . . g, 0.105 mole) and N-methyl aniline (10.8 g, 0.101 mole) were heated together at 105.degree. for 18 hr. The reaction **mixture** was poured into saturated aqueous sodium bicarbonate and extracted with benzene (30 ml). The organic layer was evaporated to give. . .

DETD . . . an ice bath. Sodium nitrite (5.5 g, 80 mmole) in water (10 ml) was added slowly over 30 min. The **mixture** was stirred an additional 1 hr at 5.degree.. The precipitated nitroso compound was filtered off, washed with 6N hydrochloric acid. . .

DETD . . . l.), and filtered. The combined filtrates were stirred for 12 hrs while air was bubbled through the solution. The resulting **mixture** was filtered. The filtrate was treated with 70% perchloric acid (10 ml) and stirred overnight. The precipitated perchlorate salt of. . .

DETD . . . (6 mg) and N-ethyl,N'-dimethylaminopropyl carbodiimide hydrochloride (6 mg). After the reaction was complete (as judged by TLC of the reaction **mixture**), 100 .mu.l of the resulting solution was separated by TLC on silica gel (20% MeOH/CHCl.sub.3). The conjugate was recovered from. . .

DETD . . . employed. Into 500.mu.l of buffer was dissolved 25.mu.l of the antibody solution and 25.mu.l of the hIgG solution and the **mixture** incubated at room temperaure for 10 min. This was followed by the addition of 25.mu.l of the Meldola Blue-hIgG conjugate. . .

DETD

Concentration of hIgG in assay **mixture**	Rate* (.DELTA.A.sub.492 in 3min.)
0	0.084
2.4 .times. 10.sup.-9	0.084
4.8 .times. 10.sup.-9	0.085
9.2 .times. 10.sup.-9	0.090
1.8 .times. 10.sup.-8	0.097
2.7 .times. 10.sup.-8	0.106
4.3 .times.. . .	

L14 ANSWER 45 OF 45 USPATFULL

ACCESSION NUMBER:	76:66499 USPATFULL
TITLE:	Fluorescence quenching with immunological pairs in immunoassays
INVENTOR(S):	Ullman, Edwin F., Atherton, CA, United States Schwarzberg, Moshe, Palo Alto, CA, United States
PATENT ASSIGNEE(S):	Syva Company, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 3996345		19761207
APPLICATION INFO.:	US 1975-591386		19750630 (5)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1974-497167, filed on 12 Aug 1974, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		